CLINICAL TROPICAL DISEASES

CLINICAL TROPICAL DISEASES

by

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AND

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From the School of Tropical Medicine, Liverpool

SECOND EDITION

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INTRODUCTION TO SECOND EDITION

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during the last few years advances in knowledge on most aspects of our subject have been cumulative and significant

A R D Adams
B G Maegraith

School of Tropical Medicine,
Liverpool

December 1959

INTRODUCTION TO FIRST EDITION

FOR some time we have felt the need for a handbook giving that information essential for the clinical diagnosis and the treatment of those diseases which occur primarily in the tropics It is to fill this need that we have ventured to produce this volume Our aim has been to supply essential facts as dogmatically and concisely as we can, where possible we have avoided speculation. We have made no attempt to provide information of an encyclopaedic nature None other than the most brief descriptions are given of the organisms causing disease, their identification, and the vectors that convey them, such information is readily available in the text books on bacteriology and parasitology

A R. D A
B G M.

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Roche Products Limited, Welwyn Garden City, Herts, England.

Symptoms and Signs in Clinical Medicine, E Noble Chamberlain, John Wright & Sons, Bristol

Textbook of Medicine, ed E Noble Chamberlain, John Wright & Sons Ltd, Bristol, 1951

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T H White

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A R D ADAMS
B G MAEGRAITH

CLINICAL TROPICAL DISEASES

I

AINHUM

DEFINITION

AINHUM is a name of South American origin but West African derivation applied to a fissured constriction, of unknown aetiology, which affects usually the fifth or fourth toes, and less commonly other digits of the feet or occasionally of the hands. The progress of the lesion is very slow, and ultimately it causes sequestration of the distal part of the affected digit.

GEOGRAPHICAL DISTRIBUTION

Ainhum occurs widely throughout the tropics and subtropics in the dark-skinned races. It is essentially a disease of negroes, and true ainhum apparently does not occur in the white-skinned races. It may

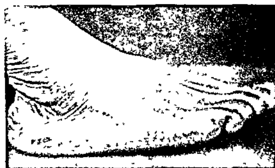


Fig. 1 a

develop in negroes who have been resident in the temperate climates for many years. Adult males are far more commonly affected than are adolescents or females.

PATHOLOGY AND CLINICAL PICTURE

The causation is unknown, but the tendency to ready keloid formation in negroes may be a contributory factor.

Ainhum starts as a fissure usually on the plantar and outer surface of the fifth toe. There is marked hyperkeratinization around the fissure, which in due course extends round the affected digit. A

constricting fibrous band finally completely encircles the digit, commonly at the level of an interphalangeal joint, but sometimes in the middle of a bony phalanx The distal part of the digit becomes bulbous, misshapen, and everted, though painless it causes mechanical inconvenience and is prone to be injured In time, often after many years, the distal part spontaneously sequestrates One toe only, and then usually the fifth, may be involved, or the condition may be bilateral; or several toes, and very occasionally a finger, may be affected.



Fig 1 b

Fig 1 a and b Ainhum of the fifth digit of the foot of an African

TREATMENT

There is no specific treatment Division of the constricting band and other conservative surgical methods of treatment are ineffective, amputation of the digit is the only satisfactory way of ending the inconvenience ainhum causes

II

AMOEBIASIS

DEFINITION

AMOEBIASIS is the name applied to a state of infection of the large intestine with the protozoan parasite *Entamoeba histolytica* In some cases the infection secondarily extends elsewhere from this primary location, for example to the liver

GEOGRAPHICAL DISTRIBUTION

Entamoeba histolytica infection of man is of world-wide distribution. It is most prevalent in ill-sanitated areas, particularly in warm climates.

AETIOLOGY

Though essentially a parasite of man, naturally-acquired *E histolytica* infections have occasionally been recorded in other primates, in rats, in dogs and, rarely, in other animals Infection, in nature, is acquired by swallowing the cysts of the parasite passed in the formed stools of those infected with it The cysts if kept moist survive for some days in faeces, if washed free from faeces and kept at low temperatures they survive longer They will not withstand drying or high temperatures, and are readily destroyed by disinfectants

Foodstuffs faecally-contaminated by uncleanly habits, or indirectly by the agency of flies, are the usual medium of infection, water is much less commonly the vehicle Cysts on being swallowed are incubated in moist surroundings as they pass down the intestine In the lowermost part of the small intestine or in the uppermost part of the large intestine each viable cyst hatches and liberates a four-nucleated amoeba The latter gives rise to a number of single-nucleated entamoebae which establish themselves in the large intestine, their precise location in some cases being in doubt (see PATHOLOGY)

The motile vegetative entamoeba is the only form of this organism which parasitizes man, it multiplies by simple division When there is [illegible]

bowel round up into a sphere, secrete around themselves a cyst wall, and appear in the formed stools as the morphologically characteristic *E histolytica* cysts It is the time spent in passage to the exterior in the faecal stream that determines whether the parasites are voided in the amoeboid or in the cystic state Amoebae, therefore, are normally

found only in loose stools, and cysts in formed stools A sudden sharp purge obviously may result in a loose stool containing cysts; but if the purgation continues amoebae only are to be found in the continuing loose stools, the cysts already formed now having been evacuated from the lower bowel and insufficient time being allowed for others to develop Cysts once formed in the lumen of the bowel do not excyst again in the same host; the cysts, therefore, are not parasitic, and they are harmless to the host in whose bowel they are formed; their presence is an indication of the infection with amoebae from which they derive

A











B C D E

Fig 2

Entamoeba histolytica A, Vegetative amoeba, B, Unstained cyst showing chromidial bar, C, D, E, Iodine-stained cysts, C and D showing glycogen mass (Diameter of cysts, 14μ)
[From F Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

PATHOLOGY

The effect of a bowel infection with *E. histolytica* varies from individual to individual Infections acquired in the temperate climates rarely cause clinical manifestations of their presence; infections acquired in the tropics commonly do so, and classically cause amoebic dysentery.

PATHOGENICITY

Various theories have been advanced to account for these facts It has been suggested that strains of *E histolytica* vary in their patho-

[illegible]

usually they are pa[illegible]
mental animals It has been stated that *E. histolytica* always causes

invasive lesions in the bowel of man and that it is the number, the extent, and the distribution of these that determine clinical patency, but post-mortem studies fail adequately to support this view Again, it has been postulated that *E histolytica* is normally a commensal parasite of the large bowel, and that it lives on the surface of the mucosa as does *E coli*; when lesions occur in the mucosa from some other cause, as when inflammatory changes occur in it, or for some yet unexplained reason, the amoebae become haematophagous and invade the tissues of the bowel wall causing pathological lesions There is at least some indication that *E histolytica* in the bowel may alternate between pathogenicity and commensalism, the classical course of amoebic dysentery tends to support this view Finally, it has been claimed that the

satisfactorily been maintained in culture in the absence of bacterial

flourish though they remain bacteriologically sterile

LOCATION AND SPREAD

The primary *E histolytica* infection is always located in the large intestine. Secondarily it may spread locally to surrounding structures within the abdomen, and it may extend directly by artificial or natural orifices to the exterior Additionally, the infection secondarily may be spread extra-intestinally by blood-borne embolism, commonly to the liver in the portal circulation, hence it will extend directly to neighbouring structures, and it may even be further conveyed embolically elsewhere

In the primary infection in the large intestine the lesions are found most plentifully at the points of stasis, that is in the caecum and at the flexures In those with a minimal symptomatology they may be confined to these points In more severe infections they occur more widely, in extremely severe infections enormous numbers of amoebae will be found in the mucosa and submucosa of the large bowel throughout its entire length In such cases the submucosa commonly is extensively fenestrated by contiguous and communicating lesions beneath large irregular areas of sloughing mucosa

HISTOLOGY

In every instance the essential pathological process is one of amoebic invasion causing a bacteriologically sterile colliquative necrosis The

amoebae secrete a ferment which liquifies the cells with which it comes into contact, the amoebae subsist on the pabulum so created, and also engorge cellular particles, more especially red cells The lesions are not inflammatory, they contain no true pus, but consist of the lysed debris of the affected tissue An amoebic liver abscess exemplifies on a gross scale the characteristic histology of any amoebic abscess, even the minute abscesses seen microscopically in the submucosa of the large

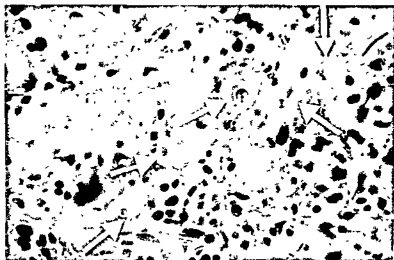


FIG 3 A section of the submucosa of the colon containing many tissue-invading *E histolytica*

intestine The contents of an amoebic liver abscess are broken-down liver substance, the classical 'anchovy sauce' content characteristic of such an abscess, most of the amoebae are invading fresh tissue around the margins of the lesion, there are but few in the central necrotic area There is no cellular walling off of the lesion, no fibrous tissue capsule is formed around it, its contents are not under pressure

A contaminant bacterial infection in due course may appear in

PROGRESS

It may be that some humoral or similar defensive mechanism checks the activities of the parasites and leads to the restriction, if not the disappearance, of the intestinal lesions during the quiescent periods [illegible]

[illegible]

tissue invasion

EXTRA-INTESTINAL INFECTIONS

An established extra-intestinal infection, however, rarely spontaneously retrogresses or resolves in the absence of specific treatment An amoebic abscess of the liver, for example, steadily extends radially beyond the liver into the abdomen and its viscera, or through the diaphragm into the chest and its contents, or to the exterior through the chest or abdominal wall The direction of its extension is governed solely by its initial location in the liver. In addition to extending locally amoebae in a liver abscess may be conveyed elsewhere embolically Amoebic abscesses due to embolism of the parasites have been described in the lungs, brain, spleen and more rarely in other tissues

Any tissue in contact with an amoebic infection, or subject to contamination with a discharge containing amoebae, may become infected with *E histolytica* A fistula or fissure *in ano* may become infected, in debilitated incontinent persons the skin of the perinaeum and buttocks may become involved Drainage wounds, such as a colostomy or following drainage of a liver abscess, may be followed by a spreading cutaneous amoebiasis around the opening

CLINICAL PICTURE

ASYMPTOMATIC INFECTION

Asymptomatic intestinal infections are the rule in those acquiring their infections in temperate climates Nevertheless it is not unusual to ascribe a most diverse symptomatology, both intra-abdominal and widely remote from the abdomen, to such infections There is no adequate justification for this.

AMOEBIC DYSENTERY

Asymptomatic infections also are acquired in the tropics, but there true amoebic dysentery is very prevalent The symptoms of this may appear within a week or two of infection or be delayed for months or years The onset of an attack of amoebic dysentery is associated with looseness of the bowel usually with evacuation of up to six or eight, but rarely more than a dozen, mucoid blood-stained motions a day Colic and tenesmus are unusual unless there is a lesion immediately

inside the anus On physical examination there may be no signs of significance. Occasionally, and especially during more acute attacks, there is palpable thickening, with tenderness on pressure, of the caecum or of the descending colon and sigmoid flexure. There is no fever or toxaemia and little prostration, so the patient if he wishes to do so *usually is able to continue his activities. The duration of an attack of* amoebic dysentery of ordinary severity may be a few days or it may last for some weeks; it then usually subsides spontaneously. There follows a period of remission which may last days, weeks, months, or even years, during this the patient not uncommonly is constipated In the quiescent period any digestive disturbances and bowel discomforts are commonly ascribed to the infection; often it is doubtful whether they can truly be regarded as due to it. Another attack of dysentery then follows. This sequence of attacks of dysentery followed by intermissions associated with constipation, which may continue for years and even for the duration of the patient's life, constitutes the classical picture of amoebic dysentery At any time complications, especially an amoebic liver abscess, may develop, they do so in about one-fifth of neglected cases

Fulminating attacks of amoebic dysentery rarely are seen in those otherwise well, but they occur frequently in debilitated subjects, who are suffering from malnutrition and from a variety of concomitant infections such as chronic malaria, hookworm disease, and other intestinal infections In such cases the destruction of the mucosa and *submucosa, and even the muscular layers and serous coat, throughout* the large bowel is extensive; the severity of the attack is in proportion, the mortality, in the absence of prompt specific treatment, is correspondingly high Complications of all kinds are prone to occur in these fulminating cases

COMPLICATIONS

Local – The direct complications of an intestinal infection are haemorrhage, often considerable, from erosion of a large vessel in the bowel wall, extension of the infection through the bowel wall, with the formation of amoebic granulomata (amoebomata); and frank sudden perforation All are rare in the classical case of average severity Amoebomata are usually the result of extension of the amoebic together with an accompanying bacterial infection Hard inflammatory tumours therefore form at the site of the lesion, and these develop and extend in the abdomen with *an accompanying pyrexia* This complication *is a serious one,* and once established does not always rapidly respond to specific anti-amoebic treatment; not uncommonly it is mistaken for malignant disease.

Remote – Of the remote complications of the intestinal infection by

far the most common is embolic spread of the amoebic infection to the liver. This occurs in from 5 to 15 per cent of all neglected cases of amoebic dysentery, it may appear even in those who, on questioning, give no history of an attack of dysentery It is most unusual for evidence of amoebiasis of the liver to appear during a frank dysenteric attack; it most commonly makes its appearance during a remission, when there is no symptomatic evidence of the intestinal infection. Its development often is slow and takes several weeks; occasionally it is extremely rapid and a large abscess may develop within a week or two The diagnosis of hepatic amoebiasis is always difficult, it is particularly so in its

small focal amoebic abscesses form, as colonies of parasites develop from these amoebae and extend their activities radially At this early stage the patient suffers discomfort and fullness in the liver area, there is usually liver tenderness, and the liver becomes engorged and enlarged, particularly in the affected lobe The temperature is irregular, the patient progressively feels more unwell, he suffers from sweats at night, and there is some leucocytosis There is never jaundice. This stage has been dubbed 'amoebic hepatitis', though in fact it is not a hepatitis It has been suggested that it is much more common than at present is recognized, and that in many or even in most cases this early

pinge and coalesce, giving rise to an irregular single abscess This steadily progresses peripherally until it destroys the whole of a liver lobe, or extends through the liver margin to adjacent tissues Discomfort and localized tenderness are now usual over the liver area, pain is referred to the tip of the right or left shoulder when the abscess is located high in one or other lobes of the liver, and there is commonly an irritant cough The amount of liver destruction and the extrahepatic extension of the abscess, and so the local signs and symptomatology, are governed by its initial location in the liver In any event the patient becomes prostrated and gravely ill, there is a swinging intermittent or remittent temperature, and there is a moderate leucocytosis of from 15,000 to 25,000 cells per cmm, the character of which is not specific The patient suffers from drenching sweats, especially at *night when sharp peaks of high* temperature occur *Bulging of the liver* may be felt below the costal margin, it may be seen in the upper abdomen, it may be visible in the intercostal spaces, or it may only be detected on X-ray screening of the diaphragm, which will be found to be raised, often irregular, and much limited in movement over the

site of the abscess If the condition is neglected the abscess ultimately will erode its way into the abdomen through the anterior abdominal or through the chest wall, or through the diaphragm into the pleura and lung in which event pulmonary amoebiasis follows Penetration of a bronchus is followed by the expectoration of material containing amoebae from the abscess, sometimes in considerable amount. A left lobe abscess not uncommonly extends into the pericardium.

DIAGNOSIS

A diagnosis of intestinal amoebiasis rests on the recovery and identification of the causative parasite in the stools, or from scrapings of those lesions which may be found sigmoidoscopically in some cases. *In asymptomatic infections, and during the intermissions in cases of* amoebic dysentery, the semi-formed or formed stools are normal in appearance On simple microscopical examination cysts of *E. histolytica* will be found in them in numbers which often vary greatly from day to day Stool examinations repeated on several (preferably 10) consecutive days are necessary before absence of the infection can confidently be assumed Various techniques may be employed for concentrating the cysts *present in formed stools* *Their employment does not replace* microscopical examination of simple wet preparations of the stools by skilled hands The adoption of concentration methods may engender a false feeling of security in diagnosis on an assumption of their infallibility

During an attack of amoebic dysentery the motions are loose or fluid, they consist of mucus and blood intermixed with faecal material in varying amount On microscopical examination actively motile vegetative entamoebae, some with engorged red cells, will be found in considerable numbers There is no cellular exudate in the absence of a heavy secondary bacterial infection of the lesions.

Suspected extra-intestinal spread of the infection always demands search of the stools for parasites to establish the presence of the primary infection Where parasites can be sought for in the actual lesions a search for them there should be made In suspected hepatic amoebiasis *needling solely for diagnosis is rarely advisable, it may be unfruitful,* no amoebae may be found in material aspirated from the centre of an abscess, and there is a danger of extending the infection and of introducing bacterial contamination The diagnosis of this condition is [illegible]

[illegible]

recognition for long periods, apparently-negative stool examinations

therefore do not justify undue delay in giving specific treatment when a clinical diagnosis is made on reasonable grounds

There is no justification in theory or in fact for the employment of 'provocative doses of emetine' as a means of diagnosis The 'therapeutic diagnosis' of intestinal amoebiasis also may be grossly misleading and has little to commend or justify it

TREATMENT

ACUTE AMOEBIC DYSENTERY

Emetine, given parenterally, is specific in the rapid arrest of an acute attack of amoebic dysentery The dosage is 1 grain of emetine hydrochloride daily, given as a single injection subcutaneously or intramuscularly The duration of treatment is governed by the severity of the attack and the therapeutic response Usually three to five injections are adequate completely to arrest an attack, under no circumstances should more than ten or a dozen consecutive daily injections be given Emetine given alone does not sterilize an intestinal *E histolytica* infection, there is nothing to be gained by giving further injections after the clinical response has been obtained To do so wastes time and drug, it exposes the patient needlessly to the risk of the toxic action of emetine, particularly on the heart, and possibly it affords the opportunity for the development of drug-fastness by the parasite

Conessine, the principal alkaloid of Kurchi (*Holarrhena* sp) bark, is an inferior and much more toxic alternative to emetine Neither emetine nor conessine injections should be given to ambulant patients, they should be confined to bed throughout the course of treatment

REMISSIONS

Having arrested the acute attack the next step is to eradicate the intestinal infection To this end a large and very varied assortment of drugs has been advocated Generally speaking, no single drug given alone so far has proved capable of sterilizing the infection with any practicable degree of certainty It has been a usual practice to give a number of drugs systematically in concert to achieve this end This procedure, though empirical, has in practice proved remarkably effective in sterilizing all but a very small minority of refractory cases of their infections

The drugs commonly employed include representatives of the following groups

(1) Emetine preparations

These are given orally and not parenterally in the belief that they exert a more effective action locally on the parasites within the intestine by this route Emetine-bismuth-iodide (E B I) is the compound

most used, but alternatively there are emetine hydrochloride and emetine periodide The selected drug is administered in gelatin capsules or enteric coated pills, as when free in the stomach it often causes immediate vomiting and is ejected. In any event later cerebral nausea follows its liberation lower in the bowel, indicating some absorption from the gut. The dose of these compounds is 1 grain thrice daily, usually on alternate days for two or three weeks.

(2) Iodo-oxyquinoline preparations

These include chiniofon (Yatren 105) which contains 26 per cent of iodine and can be given orally or, in solution, rectally; vioform, which contains 40 per cent of iodine, is insoluble so is given orally; and di-iodo-hydroxygquinoline (Diodoquin), which contains 63 per cent of iodine, is given orally for the same reason A saturated solution of chiniofon is about 4 per cent; the dose of diodoquin is three or four pills (0 21 gm) eight-hourly each day for one to several weeks

(3) Arsenical preparations

These include a number of trivalent compounds such as acetarsol (Stovarsol), Carbarsone, and Milibis (Wia); all are given orally. As most of them at least potentially are toxic a close watch must be kept for signs of toxicity On the appearance of a skin eruption the drug must be stopped at once The dose of stovarsol is 4 grains thrice daily usually on alternate days for not more than three weeks

(4) Bismuth salts

Bismuth has long been given for diarrhoea, its action may be mechanical, but at one time it was thought that bismuth subnitrate was amoebicidal. Either bismuth subnitrate or bismuth carbonate is commonly given in conjunction with more effectively amoebicidal drugs The dose of the bismuth salts is 1 drachm three or four times daily.

(5) Antibiotics

Alone of the antibiotics fumagillin has been shown to be directly amoebicidal This fact encouraged the hope that it would be of thera-

[illegible]

The tetracyline antibiotics, and others such as erythromycin and spiramycin, even when given alone, on oral administration have been shown to sterilize an appreciable proportion of cases of intestinal amoebiasis, both symptomatic and asymptomatic. These drugs, on examination *in vitro*, have not been proved of themselves to be actively amoebicidal; they apparently exert an indirectly amoebicidal effect by changing the bacterial flora present with the amoebae. Nevertheless

they promise to be of much value in the eradication of intestinal *E. histolytica* infections, especially when given in conjunction with amoebicidal drugs The dose of aureomycin or terramycin is 0 5 gm six-hourly for ten days.

COMBINED TREATMENT

One combined course of treatment, utilizing representatives of the series of drugs mentioned above, which has proved very effective in the eradication of intestinal *E histolytica* infections is as follows

(*a*) On the first, third, fifth and subsequent odd days of a three weeks period
E B I (in enteric-coated pills) 1 grain 8 hourly
Bismuth carbonate 60 grains, in milk or soda-water, 8 hourly

(*b*) On the second, fourth and subsequent even days of the three weeks period
at 8 a m A rectal washout with 2 per cent sodium bicarbonate
at 9-10 a m The foot of the bed is raised, and a retention enema of 2 to 4 per cent chiniofon is introduced into the bowel slowly Initially the amount is 4 to 7 ounces, but this later is increased to a maximum the patient can retain for at least *6 hours* with comfort (in some cases this will be 2 pints or more)

In addition on these even days of the course a 4 grain tablet of acetarsol, and 1 drachm of bismuth carbonate, are given 8 hourly Diet throughout the course is a liberal, easily assimilable one, the taking of glucose is encouraged, on the even days the patient is confined to bed for 24 hours, to encourage prolonged retention of the enema

The test of cure is examination of daily specimens of stools on a dozen occasions not earlier than a couple of weeks after the finish of treatment Ideally, the examination should be repeated at three-monthly intervals for a year, but this is rarely practicable In the event of failure, as indicated by the recurrence of parasites in the stools, the treatment is repeated, possibly with some variation in the drugs used Extremely rarely cases refractory to repeated courses of treatment of this kind will be encountered For the cure of refractory cases of this type the antibiotics mentioned earlier seemed to offer a fresh approach, this expectation has to a large extent now been fulfilled in practice

A course of 2 gms (0 5 gm 6 hourly) of aureomycin, or of terramycin, by mouth daily for 10 days usually causes the disappearance of all forms of *E histolytica* from the stools by the third or fourth day of treatment In many cases the result is permanent, but in a certain number the parasites reappear in the stools some days or even weeks afterwards. Parasitic relapse has proved to be usual after the antibiotic treatment

of a few peculiarly refractory cases of the type mentioned above. But the concurrent administration of aureomycin or, more particularly, of terramycin as already outlined with the older amoebicides has ensured a high rate of sterilization after a single treatment Some narrower spectrum antibiotics such as spiramycin, which are effective against Gram-positive but not against Gram-negative organisms, have also successfully been used for this purpose. Their employment may be preferable as thereby mass destruction of the intestinal flora, with its possible attendant consequences, is avoided It is particularly in conjunction with a combined course of treatment of these refractory cases that the antibiotics have made their greatest contribution to the treatment of amoebiasis. The indiscriminate or needless use of antibiotics is to be condemned in view of the danger of creating antibiotic-resistant strains of bacteria Their cost makes their employment in this infection even less justified in any but the exceptional case.

COMPLICATIONS

Emetine, given parenterally, is specific in the eradication of any extra-intestinal infection with *E histolytica* It is given daily as a single dose of 1 grain of emetine hydrochloride, intramuscularly or subcutaneously, over a period of twelve days. This course may occasionally require repetition after an interval, but this is unusual The early stages of amoebiasis of the liver are abruptly brought to an end by the treatment Even very large amoebic abscesses of the liver, when the parasitic infection is effectively destroyed by it, will resolve and be absorbed in many cases It may be deemed desirable to remove surgically the contents of a large abscess; this is done by aspiration, repeated as necessary, or by operative drainage; but on no account must the specific drug treatment be omitted When secondary bacterial infection of an amoebic liver abscess occurs the administration of antibacterial and antibiotic drugs may be of value, but usually surgical drainage then becomes imperative Amoebic liver abscesses only occasionally spontaneously become secondarily infected unless interfered with; it will be found that a surprisingly large proportion of them will completely resolve under specific drug treatment, provided they are not contaminated, and are treated promptly

obvious effects on the intestinal amoebic infection The dosage is 1 gm of the selected salt by mouth daily, and this is repeated for six days Chloroquine is very slowly excreted, and its action tends to be cumula-

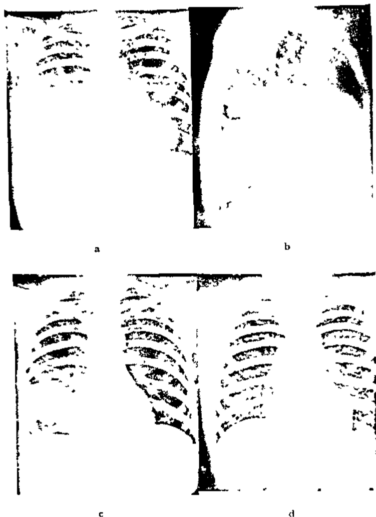


FIG 4 An enormous liver abscess

a and b Before treatment
c Twenty-four hours after aspiration of 10½ pints of amoebic liver abscess pus
d One month after a course of 12 daily injections of emetine hydrochloride gr 1

tive. This drug can be used for patients with hepatic amoebiasis who suffer from heart lesions or other conditions which contraindicate the employment of emetine, or when a course of emetine has failed to sterilize the lesion and further specific treatment is indicated.

If much pus is found in the stools, in association with amoebae, during an attack of dysentery its presence may indicate an attack of bacillary dysentery in a person already suffering from amoebic dysentery. In such cases the bacillary dysentery should first be treated with sulphonamides, and in a day or so the acute amoebic dysentery should be treated with emetine In some cases of severe amoebic dysentery with much ulceration of the large bowel there is an extensive, but non-specific, secondary bacterial infection of the lesions, with inflammatory changes in the bowel wall and the passage of pus in the stools Specific treatment of the acute amoebic dysentery with emetine will usually resolve the condition In some cases it has been found beneficial to give treatment with penicillin and the sulphonamides either prior to, or concurrently with, emetine treatment to control the bacterial infection

OTHER INTESTINAL PROTOZOAL INFECTIONS

BALANTIDIOSIS

DEFINITION

BALANTIDIOSIS is a comparatively rare condition of parasitization of the large intestine with the large ciliate protozoan parasite *Balantidium coli* The resultant disease is characterized by a severe and chronic form of dysentery

GEOGRAPHICAL DISTRIBUTION

The trophozoite of *Balantidium coli* is an oval and flattened ciliate protozoon measuring from 50 to 100 μ in length by 50 to 70 μ in breadth It produces rounded cysts, measuring about 50μ in diameter, which are passed in the stools The parasite is a common one of pigs, and occurs also in monkeys and in man Infection results from swallowing the cysts passed in formed stools by the reservoir hosts, principally the pig It has no restriction in geographical location

PATHOLOGY

While, as in the case of *Entamoeba histolytica*, *B coli* in asymptomatic cases of infection may dwell within the lumen of the large bowel, in those cases presenting symptoms it is a tissue-invading organism On histological section parasites can be seen lying in the mucosa and submucosa of the wall of the large intestine, their presence causes the development in the overlying mucosa of irregularly rounded ulcers, which have undermined edges and a base composed of necrotic material In addition to these limited areas of necrosis haemorrhagic areas without ulceration are to be seen in the mucosa

CLINICAL PICTURE

The infection in some cases is asymptomatic, and is detected only incidentally on examination of the stools In most cases of balantidiosis there is dysentery with the passage of bloody mucoid stools, clinically the dysentery much resembles severe amoebic dysentery The diagnosis during such an attack is made by finding the trophozoites of the parasite in the stools, during intermissions the cysts will be found

TREATMENT

There is no treatment which consistently is effective in eradicating the infection Arsenicals, such as stovarsol, by mouth, organic silver preparations, given as retention enemata, and various dyes, such as methylene blue, also given as enemata, have at various times been stated to sterilize the bowel infection The tetracycline antibiotics also are claimed to exert a specific action on the causative infection

FLAGELLATE DIARRHOEA

A number of flagellate protozoa commonly parasitize the human intestine *Giardia lamblia* is one of those which has been stated on occasions to cause clinical manifestations of its presence in the form of a watery or of a fatty diarrhoea. While this organism cannot be regarded as a true pathogen, the fact that it adheres by means of a sucking disc to the mucosa of the duodenum lends some credence to the view that it may give rise to duodenitis when present in very large numbers. It has also been stated that it may invade the biliary passages by ascent of the common bile duct Whether the parasite is responsible for diarrhoea, or whether its presence in enormous numbers in loose stools is a sequel of the diarrhoea, is by no means clear. The diarrhoea is not of a dysenteric type

[illegible]

tion is detected by examination of the stools.

III

ANCYLOSTOMIASIS

DEFINITION

HOOKWORM infection Infection with the nematodes *Ancylostoma duodenale* and *Necator americanus* with or without physical signs including hypochromic anaemia

GEOGRAPHICAL DISTRIBUTION

Hookworm infection is found under insanitary conditions in temperate regions and in hot damp areas throughout the tropics and subtropics

A duodenale is common in temperate climates, especially in parts of Southern Europe and the Middle East, China, Japan and North Africa From time to time it has appeared in mining areas in colder parts of Europe

N americanus is widely spread in the tropics, including West, East, Central and South Africa, North America, Panama and South America It was at one time common in the southern United States, into which it was introduced from Africa

Both worms occur in many districts in the Far East, India, Africa and South America

Hookworm disease may occur at considerable altitudes It has been recorded, for instance, in populations at over 6000 ft

AETIOLOGY

Hookworms are nematodes belonging to the family *Ancylostomidae* Man is the natural host and harbours the adults in the small intestine Eggs are passed in the faeces Human infection is caused by *A duodenale* and *N americanus* which complete their life cycle in man Infection of the subcutaneous tissues with *A braziliense*, the hookworm of dogs and cats, may also occur in man, in this case the worm does not reach maturity

The adults of *A duodenale* are small, measuring between 8 and 13 mm The female is only a little larger than the male The body is slightly curved and tapered at both ends, the buccal cavity has pointed clawed teeth

Adults of *N. americanus* are slightly smaller The worms are fine and tapered, the head in both sexes is bent back in a short reverse curve which makes for easy identification The buccal cavity contains two chitinous plates

FLAGELLATE DIARRHOEA

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Diagnosis of the infection is made by finding cysts of the parasite in [illegible]

[illegible]

tion is detected by examination of the stools

N. americanus or 20 *A duodenale* will cause no clinical symptoms Severe symptoms are produced when the load exceeds 500 of the former and 100 of the latter In the presence of food deficiencies the critical figures for the load are probably much lower

The worm attaches itself to the mucosa of the upper part of the small intestine, and absorbs blood from the submucous tissues The amount of blood lost in this way depends on the number of worms Some blood is also probably lost as a result of oozing from ulcerated areas in the intestinal wall

The main pathological effects of hookworm infection arise primarily from blood loss and the consequent development of anaemia It has been calculated that a single worm accounts for the loss of 0 2 to 0 5 ml blood per day

During migration of the worm from the point of entry to the intestine there may be changes in the tissues through which the larva is or has been passing In the epithelium and subcutaneous tissues near the site of entry, for instance, there may be a papular vesicular change Small

Anaemia As has already been pointed out, there may be no blood changes even in a heavy infection When anaemia occurs it is hypochromic and microcytic It arises chiefly from the removal of blood by the worm, from the bleeding due to gut ulceration and possibly to some extent from ineffective reconstitution of the blood, resulting from iron deficiency The characteristics of the blood picture may be modified by various dietary deficiencies In severe infections the marrow exhibits intense erythropoietic hyperplasia

White blood cells There may be a mild leucopenia with relative lymphocytosis On the other hand, there may be a pronounced leucocytosis Eosinophils may account for as much as 30 per cent of total white cells The eosinophilia is most marked in early cases

CLINICAL PICTURE

Mild or moderate infection with hookworm often exists without overt clinical signs and is apparently consistent with good health, pro-

tomiasis, particularly anaemia

In many regions large numbers of the population are infected without any overt signs, in others, with apparently the same worm load, but also ill-nourished, the classical picture develops It is not surprising

LIFE CYCLE IN MAN

Eggs are passed in the faeces of an infected host. In warm moist shady conditions, with a suitable soil, the eggs hatch in about 5 days, in less favourable conditions up to 3 weeks. The actively motile larvae so produced migrate to the subsoil and feed in the mud or sand on bacteria and organic matter.

After two moults the sheathed larvae reach the surface, migrating upwards rather than laterally, and may eventually penetrate the human skin, losing their sheath and progressing along the subcutaneous tissues to the lymphatics and blood vessels. By the third day after penetration the larvae usually reach the lungs, where they escape from the blood vessels to the alveoli and set up a focal inflammatory reaction. They eventually reach the bronchi and trachea, and are swallowed, finally reaching the upper part of the small intestine and maturing 3 to 5 weeks after the infection.

TRANSMISSION

Transmission of hookworm infection may occur wherever faeces are allowed to remain in contact with damp soil at a suitable temperature varying from 75° to 90° F Loose sandy soils are most favourable; clay is unsuitable since it prevents migration. Moisture is essential Some infective larvae will survive in the soil for weeks under suitable conditions

Larvae enter the human subject through the skin In most cases the entry occurs through the legs or feet, often between the toes, and occasionally through the skin of the hands It will occur, however, through any part of the body suitably exposed

GENERAL

All races are equally susceptible to infection.

[illegible]

infected

PATHOLOGY

The pathological effects of infection depend on the worm load and the nutritional condition of the host. In the majority of cases the latter is probably the deciding factor in determining the host's reaction to the infection.

Moderate worm loads can be carried without symptoms by most individuals. It has been reckoned that infection with less than 100

Cardiac palpitation is common and the heart may be dilated Changes in the hair, including dryness, loss of curl and pigment, associated with hookworm infection by some authors, probably arise from concomitant malnutrition

The total white count is usually within normal limits There is often a high eosinophilia (15 to 30 per cent) which tends to disappear as the condition advances

Epigastric discomfort is present in most cases The pain may suggest duodenal ulceration in the early stages In the anaemic patient there is often gastric hyperacidity, followed later by achlorhydria Most patients are constipated Diarrhoea occurs in some Macroscopic blood in the faeces is uncommon

Characteristic of the infection are lassitude and mental dullness, which may dominate the picture in the severe case or be the only obvious signs of illness in the mild case, appreciated only after the return to health following treatment

Albuminuria is often present in severe cases Casts may or may not accompany it

The signs of heavy infection with hookworm usually develop slowly Occasionally they may appear rapidly, the syndrome becoming pronounced in a matter of weeks from the first local signs of infection In such acute cases the gastro-intestinal symptoms are usually severe There may be nausea and vomiting, diarrhoea is common and the faeces contain mucus and sometimes a little blood Eosinophilia may be high In some cases the anaemia may be well advanced before the first appearance of eggs in the faeces Treatment in such cases usually results in the passage of large numbers of worms The symptoms are likely to be most severe in *A duodenale* infection

COURSE AND PROGNOSIS

Severe cases in children may terminate fatally, particularly if the anaemia is allowed to continue untreated for some time Milder cases lead slowly to pronounced physical and mental retardation which respond well to treatment Acute cases also respond well

The duration of life of the adult worm in the intestine is uncertain A given infection may apparently continue for years after the patient has left the endemic area On the other hand many cases in similar circumstances recover in a few months It is possible that in the former case the worm load is kept going by self re-infection

The vast majority of infections do not result in marked clinical changes In any heavily infested area in which nutrition is satisfactory the bulk of those infested will show no signs whatever In areas in which deficiencies occur in the diet, and particularly in those in which there is a seasonal or continuous lack of first class protein, moderate infections

therefore that it is often almost impossible to assess the genuine cl
effects of hookworm infection

Migration of larvae: The migration of larvae after penetration
skin may give rise to local changes which are easily recognized

The patient complains of intense itching in the area affected
becomes erythematous and slightly oedematous. This is soon foll
by a papular vesicular dermatitis which subsides in the course of
two weeks unless secondarily infected This is called 'ground itch
is found commonly on the feet, ankles and hands, in that order,
commonest with necator infestations. Many subjects may nc
affected with ground itch.

Pulmonary Changes Minute haemorrhages may occur in the lun
the time the hookworm larvae break out from the blood strea
the alveoli These may be followed in heavy infections by some
cellular reaction and signs of pulmonary involvement In the maj
of cases the pulmonary signs are, however, minimal and mucl
obvious than in infections with other helminths, such as ascari
the more acutely developing case, there may be some bronchitis
cough and even expectoration of blood-stained sputum conta
eosinophils.

THE EFFECTS OF INTESTINAL LOCALIZATION OF ADULTS

The adult hookworms establish themselves in the mucosa anyw
between the duodenum and the upper ileum. When they are pr
in large numbers considerable amounts of blood may be drained
the patient. When the infection is light the loss of blood has litt
no effect on the host, in whom regeneration can cope with the los
more severe cases, either because of heavy worm load or becau
other factors, particularly pregnancy, growth and malnutrition,
regeneration of the blood cannot keep pace with the bleeding
anaemia develops

In the average severe case the red cell count ranges from 2
million cells per cu mm The colour index is well below 1.0 The
are hypochromic, usually microcytic and there is some aniso- and p
locytosis The picture is essentially that of secondary anaemia assoc
with iron deficiency. All degrees of anaemia may be found and
erythrocytic picture may not always appear as above Complica
factors related to nutrition are nearly always present; there may
be some macrocytosis which obscures the underlying *secon*
character of the anaemia

Severe anaemia is seen most commonly in children. The patie
pale The face is often puffy and there may be oedema of the
tremities The abdomen is distended; there may be ascites.
patient complains of breathlessness on exertion and increasing lassit

The differential diagnosis of ancylostomiasis should be settled by the discovery of the worm or eggs In an endemic area stools must always be examined in anaemic individuals It is wise also to search for evidence of ancylostomiasis in cases with gastrointestinal symptoms suggestive of duodenal ulcer

The characteristic picture of the pot-bellied oedematous anaemic child is unlikely to be missed The finding of the worm in such cases should not blind the observer to the tremendous importance of nutritional disturbances and deficiencies in the genesis of the clinical picture

TREATMENT

In many cases it is difficult to assess the importance of hookworm infection in the production of the clinical picture Where the worm load is very heavy there is an obvious indication for vermifugation Where it is moderate or light it may or may not be necessary to remove the worms

Most anaemic cases with a moderate worm load will probably owe their condition more to malnutrition than to the worm infection Treatment of the latter alone will under these circumstances not necessarily lead to clinical improvement

In the treatment of infections, therefore, two factors must be borne in mind, i e. (i) the effect of the worm load itself, and (ii) the effect of environmental and nutritional factors

There is no simple guide to the indications for treatment Each case must be decided on its merits As a working rule, however, it may be said that clinical effects may arise, other things being equal, if the calculated worm load exceeds 100 It must be realized, however, that loads of this size and considerably greater may exist without apparent ill effects and that smaller loads may be significant if the nutritional state is poor

In all cases undergoing treatment the whole question of nutrition must be considered It often happens that proper adjustment of the diet leads to recovery of the clinical state even without treatment of the infection Similarly, vermifugation may remove the infection without any improvement unless the nutritional condition is restored

TREATMENT OF INFECTIONS

The following regimes may be used when hookworm infection only is present If, as commonly happens, ascaris infection is also present, this should be treated simultaneously, using combined therapy (see p 27)

Recent studies suggest that Alcopar is effective against both hookworm and ascaris infection Dosage is given on p 481

may be accompanied by severe clinical signs which may respond to treatment only when the diet has been adequately readjusted.

DIAGNOSIS

fae

Eg

from time to time

The Eggs The identification of hookworm eggs is easy. The eggs of A. *duodenale* measure 40 to 60 μ They are oval, with a smooth transparent covering The eggs when passed usually contain developing embryos consisting of 4 to 8 cells. The eggs of N. *americanus* are larger (60 to 70 μ) but otherwise similar

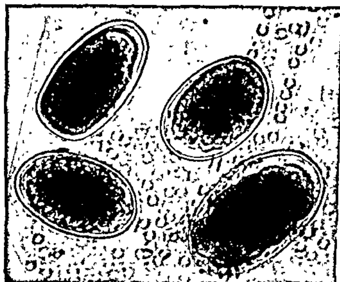


FIG 5 *N americanus* ova
[Courtesy of *Annals of Tropical Medicine and Parasitology*, School of Tropical Medicine, Liverpool]

Estimation of Worm Load Weigh 2 gm of faeces Mix through a sieve with 60 ml saturated salt solution Agitate and count in a MacMaster counting chamber Volume counted in chamber is 0 3 ml Total volume of suspension is 60 ml (containing 2 gm faeces). Hence number of eggs per gram = number counted in chamber × 100 Each female worm is represented by about 50 eggs per gram of faeces

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Tetrachlorethylene This drug is usually made up in gelatin capsules containing 1.0 ml. It may be given in a spoon mixed with sugar, or [illegible]

half ounce). After purgation the drug is administered in two equal portions given half an hour apart.

The saline purge is repeated 1 to 2 hours after the last dose.

The drug is badly tolerated by alcoholics and is contraindicated in gastroenteritis and chronic constipation

A carbohydrate-rich diet is sometimes advised for some days before and after treatment, in order to reduce toxicity. Fats and oils should be withheld for 2 to 3 days before and after treatment. The drug is far less toxic than carbon tetrachloride. *It should not be used alone in the presence of ascaris infection* since it may cause these worms to migrate actively *and lead to intestinal obstruction.*

The treatment can be repeated after a fortnight if the first treatment is unsuccessful

Dose

Adults Total dose. 2.0 to 3.0 ml
Children For each year of age 0.15 ml

Hexylresorcinol: The drug is supplied in capsules containing 200 mgm

The patient is prepared as for tetrachlorethylene The drug is administered in a single dose after preliminary purgation. The purge is repeated in 1 to 4 hours after treatment

A fortnight should elapse between successive treatments if these are required

Hexylresorcinol is relatively non-toxic Capsules should be swallowed whole and not broken up by the teeth, since the drug may cause intense irritation and excoriation of the buccal mucosa

Dose:

Adults. Total dose 1.0 gm
Children Age 9 to 13, 800 mgm
Age 7 to 9, 600 mgm
Under 7, 400 mgm

Oil of Chenopodium The drug may be given neat or in gelatin capsules

The patient is prepared as for tetrachlorethylene The drug is given in two equal fractions at intervals of one half hour. A saline purge is given 1 to 2 hours later

Treatment should not be repeated for at least a fortnight.

The effective therapeutic dose is close to the toxic dose and serious consequences, even death, may occur from over-dosage

Dose

Adults Total dose not more than 1 0 ml
Children For each year up to 16, 0 05 ml

Oil of Chenopodium and Tetrachlorethylene This course is commonly used when ascariasis is also present. Hexylresorcinol may be used alone against the combined infestation

The drugs are given together as a single dose as for hexylresorcinol. They may be suspended in liquid paraffin if capsules of the tetrachlorethylene are not available, or difficult to administer as in children

Dose

Adults. Oil of chenopodium, 0 5 ml to 1 0 ml
Tetrachlorethylene, 2 0 ml.
Children Oil of chenopodium, 0 025 ml per year of age
Tetrachlorethylene, 0 10 ml per year of age

Hexylresorcinol and tetrachlorethylene are both more effective than oil of chenopodium and may be expected to deal with 75 to 95 per cent of the adult worms

After treatment the worms are usually passed within 3 days and in this period the faeces should be carefully examined for them, and the numbers checked against the estimated load

Most cases require only one course of treatment since the load remaining is usually too small to bother the patient Total eradication of worms may be achieved only after repeated treatment

TREATMENT OF THE ANAEMIA AND DEFICIENCIES

The anaemia of ancylostomiasis originates in blood loss through the feeding of the adult worms in the intestine The condition is aggravated in severe cases by the concomitant loss of iron and the failure of its replacement due to inadequate diet and continued bleeding The body reserves of iron are thus frequently depleted and blood regeneration becomes faulty

In some cases there is an additional element of deficiency in blood regeneration arising from dietetic deficiencies, which may tend to ind[illegible]

T[illegible]
cor[illegible]
general, the loss of blood must be stopped by the removal of the bulk of the parasites, and the regeneration of blood must be stimulated and maintained by iron therapy and readjustment of dietary deficiencies

The treatment of the worm load should be the primary aim in the average severe case In very severe cases transfusion and iron therapy may first be required In such cases the drug of choice for elimination

of the worms is probably hexylresorcinol on account of its low toxicity.

Iron in the ferrous form may be administered intravenously or by mouth. Most cases absorb it readily after oral dosage and regeneration of blood frequently occurs promptly after its use.

Adjustment of the diet is basic in the treatment of ancylostomiasis. The administration of liver or its extracts orally or parenterally may often be more effective in relieving the anaemia than meat or milk. Return to a well-balanced protein diet as soon as possible is indicated. The combination of liver and iron therapy often has a very stimulating effect on blood regeneration even without the removal of the worms

TREATMENT OF GROUND ITCH AND CREEPING ERUPTION

Local treatment of ground itch requires the application of antiseptics with the object of reducing the risk of secondary infection. The itching is difficult to relieve

PROPHYLAXIS

The control of hookworm disease depends on sanitation and mass treatment Where the latter is effective and faeces are not allowed to remain in surroundings suitable for the development of infective larvae, there will be no infection In districts in which sanitation has been recently enforced, an attempt should be made at mass treatment with the object of removing the infection from the community. Individual prophylaxis in infected areas includes the avoidance of infection by the protection of the feet, for example, by the insistence on wearing shoes.

IV

BACILLARY DYSENTERY

DEFINITION

BACILLARY dysentery is due to infection of the large intestine with one of the pathogenic species of bacteria belonging to the genus *Shigella*. The infection is a local one of the bowel wall, and it does not spread systematically. The disease caused by it is characterized by colitis, with severe bloody diarrhoea and fever, its course is acute, certain complications remote from the bowel are the result of absorption of toxins. The mortality is high with certain infections.

GEOGRAPHICAL DISTRIBUTION

World-wide and particularly prevalent when sanitation is defective or lacking. The most severe forms of bacillary dysentery are especially associated with the tropics.

AETIOLOGY

Infection with organisms of the genus *Shigella* in nature is peculiar to man. The infection results from swallowing the bacilli, usually in food or water contaminated with infected human faeces. Insanitary and uncleanly habits, and the activities of flies, facilitate their dissemination by mechanical transference. The bacilli are voided in great numbers in the stools of those actively suffering from an attack of bacillary dysentery, in some cases they continue to be passed in the stools for some time after the attack, symptomless carriers are an occasional source of infection. Under suitable conditions bacillary dysentery tends to occur in epidemics, the severity of these and the associated mortality depend on the species and strain of the causative *Shigella* infection.

Species and varieties of the genus *Shigella* [illegible]

[illegible] ticularly found in temperate climates. The other species and varieties cause manifestations of all degrees of severity between these two extremes. The identification and the typing of the organisms, which are recovered by bacteriological culture of the stools, are matters for a properly equipped and staffed laboratory.

PATHOLOGY

On swallowing dysentery bacilli these may be destroyed by the physiological barrier of the normal gastric juice This, however, is readily broken down, for example by dilution; the organisms then pass into the small intestine and reach the large bowel. In the large bowel they multiply with great speed, in a severe infection they largely supplant the normal flora of the bowel. Toxins liberated by the bacteria cause inflammatory lesions in the mucosa, which in virulent infections is damaged and is invaded by the organisms In clinically mild cases of dysentery, however, there is nothing more than a mild inflammation and engorgement of the mucosa of the large intestine; this is of short duration and resolves when the infection is overcome, often within a few days In more severe cases the inflammation is extensive and pronounced; there is marked engorgement and oedema of the mucosa, and the crests of the folds of the mucosa, lying transversely across the bowel, are denuded giving rise to narrow and shallow serpiginous ulcers ('snail track' ulcers) These ulcers heal with minimal scarring as the infection is overcome and the inflammation subsides, the bowel ultimately is restored substantially to normal In the most severe attacks of dysentery, commonly due to *S shigae* infections, the whole process is exaggerated and the mucosal destruction is deeper and more extensive. Considerable areas of mucosa and submucosa slough; if the patient recovers from such an attack these gross areas of ulceration are repaired by the formation of scar tissue, this contracts, causing kinking and deformity of the bowel Moreover, being covered only by simple epithelium, and being comparatively avascular, the scars are readily injured and secondarily infected by a variety of bacterial organisms The end result may be a chronic post-dysenteric colitis, from which the primary and

causative *Shigella* infection in the bowel The organisms are passed continuously or intermittently in the stools, from which they can be recovered by culture on suitable media The lesions in the bowel are of a chronic inflammatory nature, with engorgement, oedema and recurring ulceration following abscess formation in the mucosa, blockage of crypts containing mucus-secreting glands during the inflammatory process results in their distension and the formation of 'retention cysts' The abscesses and cysts contain dysentery bacilli, and the liberation of their contents accounts for the periodic appearance of the organisms in the stools

Absorption of toxins from the intestine is held to be responsible for a variety of inflammatory lesions remote from the intestine These lesions, which invariably are bacteriologically sterile and never suppurate,

affect in particular the eyes, the joints, and peripheral nerves Conjunctivitis and irido-cyclitis, polyarthritis, and peripheral neuritis, are common complications or early sequelae of an attack of bacillary dysentery.

CLINICAL PICTURE

Predisposing causes of bacillary dysentery include any form of enteritis or colitis. Most Europeans on first going to the tropics suffer from attacks of diarrhoea These are commonly referred to as 'the squitters', 'the trots', 'Gyppy tummy', 'Delhi belly', and so forth They may be precipitated by changes in environment, climate and diet, by alterations in the intestinal flora, or by the inhalation and ingestion of trauma-producing matter such as dust and sand Many of them doubtless are very mild attacks of bacillary dysentery, which pass unrecognized as such

The incubation period of bacillary dysentery is short It does not exceed a week, usually is less than three days, and may even be less than twenty-four hours The onset of an attack of average severity is sudden, it is associated with abdominal discomfort, sometimes nausea and vomiting, and a rise in temperature Within a few hours there are colicky pains and sharp diarrhoea The first motion passed contains faecal material, but thereafter there is little of this and the motions largely consist of tenacious blood-stained mucus which is voided in small amounts at very frequent intervals The naked-eye appearance of the motions has been likened to that of 'red currant jelly' Their

intermittent, continues throughout most of the attack, this lasts from one to as much as three weeks, according to its severity As the infection is overcome the temperature declines, the intensity of the symptoms diminishes, the amount of blood in the motions lessens, and their number decreases Visible blood vanishes from the motions which, though still consisting largely of mucus, become bile-stained before becoming more normal in appearance and consistency with the end of the attack and the entry upon convalescence

Mild and ambulatory cases of bacillary dysentery are very common and often escape specific diagnosis Fulminating cases of the disease are particularly associated with Shiga infections In these all the clinical manifestations are exaggerated The toxaemia and prostration are profound, large amounts of blood may be lost in virtually continuous fluid motions, these contain shreds and pieces of necrotic mucosa; their appearance has been likened to that of 'raw meat choppings' In such

cases the temperature may rise in a day or so to a very high level, or it may not rise at all but become subnormal and the patient dies within a short time.

In a febrile, toxaemic and exhausting disease such as this, which is associated with the continuous loss of fluid, such complications as dehydration, peripheral circulatory failure, and renal failure may be expected. These are particularly evident in children and in the elderly, to both of whom bacillary dysentery is a serious and not uncommonly fatal disease. In young children the onset of the disease is not unusually associated with convulsions.

It is towards the end of the acute attack or in early convalescence that the common systemic complications, inflammation of the eyes, joints, or peripheral nerves, make their appearance. These, though not of themselves serious, can cause much discomfort; they resolve after some days or within a week or two, and leave no permanent evidence of their presence.

The intra-abdominal complications which may be encountered include severe intestinal haemorrhage, perforation with acute peritonitis, and chronic peritonitis, all these are rare. More rare still are pneumoperitoneum, and portal pyaemia with multiple abscess formation in the liver.

Haemorrhoids, which may thrombose, or rectal prolapse are liable to occur during an attack of bacillary dysentery as in attacks of diarrhoea of any causation.

DIAGNOSIS

The clinical picture clearly suggests the diagnosis, especially during an epidemic of bacillary dysentery. Simple microscopical examination of the stools should invariably be made; this will reveal the presence of an inflammatory exudate. In this exudate will be found macrophage cells; these must clearly be differentiated from amoebae. Culture for the causative organism should also be done. Material for this is best obtained by rectal swabbing; alternatively, suitable portions of the motions may be selected for the purpose without delay after passage. When the inoculation of media cannot be performed at once, the selected portion of stool may be put in 30 per cent glycerol in isotonic

TREATMENT

A number of antisera at various times have been prepared against sundry species and types of Shigella, none of these has proved to be of

organism A highly concentrated Shiga anti-toxin is now available, 100,000 units or more of this, given intravenously early in the disease, are said to diminish the severity of the toxaemia in cases of Shiga infection The identification of the organism obviously cannot be awaited before treatment is begun, so it is not unwarrantable in severe cases of toxaemia due to suspected Shiga infection to give this anti-toxin at once This temporarily may modify the severity of the toxaemia, but it must be followed without delay by specific drug treatment to control the infection

Early in World War II American workers observed that sulphanilyl guanidine (sulphaguanidine) when given orally to small animals profoundly reduced and modified the bacterial flora in their stools They found that the drug was absorbed only to a minor extent from the intestine, and concluded that it exerted its action there locally Bacillary dysentery involves an infection confined to the intestine A number of children suffering from proven bacillary dysentery were treated with this drug, and the results were extremely good The patients responded within a day or two to the treatment, and rapidly became convalescent Their infections were eradicated and they were cured Confirmation of the rapidly effective specific action of sulphaguanidine on bacillary dysenteric infections in adults was soon forthcoming The dosage advocated was an initial one of 0 1 gm per kgm of body weight, this was followed by half this dosage repeated at 4 hourly intervals until the number of motions voided each 24 hours was four or less, it was then continued at 8-hourly intervals for another 3 days For a normal-sized adult a round figure for sulphaguanidine dosage is an initial one of 6 gm, followed by 3 gm 4-hourly, and finally 8-hourly as convalescence is established The drug should never be given for more than 10 days

Succinyl sulphathiazole (sulphasuccidine) and phthalyl sulphathiazole (sulphathalidine) are later compounds with the similar property of slow intestinal absorption, these are even more effectively bacteriostatic than is sulphaguanidine and may be used in its place Some of the freely absorbed sulphonamides are prone to cause crystalluria, this tendency is aggravated in a febrile disease associated with considerable fluid loss, such as bacillary dysentery especially in a hot climate The very slow absorption from the gut of compounds such as sulphaguanidine, sulphasuccidine, or sulphathalidine, greatly diminishes this risk

of crystalluria and its sequel, renal obstruction These compounds, therefore, have much to commend them for routine use in the specific treatment of the bacillary dysenteries, particularly under field conditions in the tropics

Nevertheless, a number of the freely absorbable sulphonamides have proved as therapeutically effective as the slowly absorbed sulphonamides in bacillary dysentery Indeed, some workers consider sulphadiazine to be the most effective of all sulphonamides in the treatment of this condition The dosage of sulphadiazine is up to a maximum of 8 gm daily; it is given in divided doses at 4-hourly intervals; the risk of its causing renal obstruction must always be remembered, and should be diminished as far as is possible by correcting dehydration, by giving copious fluids, and by an endeavour to keep the urine alkaline. In the event of oliguria or anuria the drug must immediately be stopped; renal lavage with warm water must promptly be done to clear the obstruction if it persists

The development by certain strains of *Shigella* of sulphonamide resistance has on occasions been recorded. Inadequate treatment with sulphadiazine of successive cases of infection with a strain of Flexner Z in an institution eventually caused it to become completely refractory to this drug While excessive and unduly prolonged sulphonamide dosage is undesirable, inadequate treatment is equally to be avoided.

Of the antibiotics neomycin seems to be the most consistently effective against the *Shigella* group of organisms. Streptomycin, chloromycetin, the tetracyclines, and polymixin are less regularly so *S. sonnei* infection does not respond satisfactorily to sulphonamide treatment but yields to chloromycetin, which therefore is the drug of choice in this case Generally, with this exception, antibiotic treatment is inferior to sulphonamide treatment of the bacillary dysenteries, for this and other reasons, the antibiotics should be reserved for the control of sulphonamide-resistant strains of the causative organisms

the bacillary infection

V

BARTONELLOSIS

DEFINITION

BARTONELLOSIS, Oroya fever and verruga peruana, or Carrion's disease, are due to infection with a bacteriform organism *Bartonella bacilliformis* The infection is transmitted by female sandflies (*Phlebotomus* spp), which develop an intestinal infection with the organism and convey it by their bites The disease following infection of man is characterized by two distinct and consecutive clinical syndromes. The first is the stage of Oroya fever, a severe febrile anaemia, the second, the verruga peruana stage which follows is characterized by the appearance of an eruption consisting of small haemangioma-like tumours. The mortality in the untreated is about 40 per cent during the first stage, and in some epidemics it has been much higher The mortality is rarely due to uncomplicated Oroya fever, commonly it is the result of a complicating septicaemic *Salmonella* infection, to which these patients' resistance is peculiarly lowered

GEOGRAPHICAL DISTRIBUTION

The disease is remarkably restricted in its distribution, being confined to the continent of South America There it has been found on the eastern and the western slopes of the Andes in certain narrow valleys in Peru, Ecuador and Colombia, usually between 2000 and 10,000 feet above sea level

AETIOLOGY

The causative agent, *Bartonella bacilliformis*, in nature has been recovered only from man and the insect vectors It is a very small extremely pleomorphic bacterium-like organism, which can be found in large numbers in red cells and in cells of the reticulo-endothelium throughout the body during the Oroya fever stage of the disease It takes the form of minute rods or rounded bodies measuring up to 2 µ in their greatest diameter, the rods often are slightly curved, they occur singly, in short chains, or in clusters The organisms are Gram-negative, they stain well with the Romanowsky stains, taking a reddish-violet colour, some appear to be bipolar They can be cultured in living tissue cultures, on blood agar, on Noguchi's leptospira and other special enriched media In fresh preparations of naturally infected blood, and in young cultures *in vitro*, they show motility

For some time before it was actually proven it was believed that

of crystalluria and its sequel, renal obstruction. These compounds, therefore, have much to commend them for routine use in the specific treatment of the bacillary dysenteries, particularly under field conditions in the tropics

Nevertheless, a number of the freely absorbable sulphonamides have proved as therapeutically effective as the slowly absorbed sulphonamides in bacillary dysentery. Indeed, some workers consider sulphadiazine to be the most effective of all sulphonamides in the treatment of this condition. The dosage of sulphadiazine is up to a maximum of 8 gm daily, it is given in divided doses at 4-hourly intervals, the risk of its causing renal obstruction must always be remembered, and should be diminished as far as is possible by correcting dehydration, by giving copious fluids, and by an endeavour to keep the urine alkaline. In the event of oliguria or anuria the drug must immediately be stopped; renal lavage with warm water must promptly be done to clear the obstruction if it persists

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As in other acute infectious diseases, Cortisone may be used during the earliest days of treatment of fulminant cases, especially of Shiga's infection, to avoid a fatal outcome before the specific treatment controls the bacillary infection

while others are free. A high proportion of all endothelial cells contain masses of *B bacilliformis.*

In the second, eruptive or verruga peruana, stage the lesions of the skin consist at first of newly formed blood vessels lying in oedematous connective tissue In them there are haemorrhagic foci, and there is a marked proliferation of endothelial cells A striking feature is the small bore of the numerous blood vessels in comparison with the thickness, often several cells deep, of their lining endothelium, endothelial cells also proliferate outside the vessels and form angioblastic tumours which compress and may obliterate the lumina of the contained vessels In older lesions fibroblasts invade these islands of cellular proliferation and form collagen fibrils among which lymphocytes, plasma cells and leucocytes appear In some lesions the overlying epidermis disappears, and the surface is covered by little more than organized blood clot Secondary bacterial infection causes the development of pyogenic foci in the lesions

Subcutaneous nodules, histologically similar to the cutaneous lesions, also form, these often undergo central necrosis In the cytoplasm of the endothelial cells of all the cutaneous and subcutaneous lesions *B bacilliformis* can be found, but they are not present in such numbers as in the tissues during the initial non-eruptive, or Oroya fever, stage

CLINICAL PICTURE

It has now clearly been established that Oroya fever and verruga peruana are stages of the same disease The former normally, but not invariably, precedes the latter, but it never follows it The eruptive, or second, stage though commonly a sequel of the first may appear in its apparent absence, possibly in such cases the non-eruptive Oroya fever stage is so unusually mild as to escape diagnosis

Oroya fever The incubation period of Oroya fever is variable, it ranges from 16 days to 4 months, usually it is three or four weeks

The onset may be sudden, with high fever and rigors, usually it is insidious, with increasing malaise, headache, severe pains in the joints and bones, and intermittent or remittent fever Nausea, vomiting and diarrhoea are present in association with anorexia and thirst Anaemia becomes evident early, and it progresses steadily until it is very severe and clinically obvious The blood pressure falls, cardiac murmurs are heard, there is a marked increase in the respiration rate, and the patient suffers from vertigo on attempting to rise The diminution in the number of red cells causes the skin to become wax-like and the mucous membranes blanched The patient is prostrated, and may be delirious. Pains are troublesome and continuous, they involve in particular the joints and the epiphyses of the long bones

bartonellosis was conveyed by certain sandflies. *Phlebotomus verrucarum*, *P peruensis*, and *P noguchii* are all vectors, there is reason to believe that other species of *Phlebotomus* may be vectors; but of them all *P. verrucarum* is the most

tant. Only

crepuscular

pure cultures of *B. bacilliformis* have been obtained from the guts of female *P. verrucarum*, freshly caught wild sandflies of this same species when fed on monkeys have produced an infection in them. Transmission takes place in the act of feeding, possibly through infection of the proboscis.

Human bartonellosis normally is endemic in well-defined localities, under certain conditions, such as the congregation of non-immunes in an endemic area, it can become epidemic. A classical example of this occurred in 1870, when a severe and extensive epidemic occurred among workmen building the Central Railway between Lima and Oroya; it is estimated that over 7000 individuals died in this outbreak.

Persons of all ages and both sexes are affected; among the natives of the endemic areas the disease is one of childhood, and as infection confers immunity to reinfection its occurrence in adults is correspondingly low.

PATHOLOGY

In the first, non-eruptive or Oroya fever, stage the essential pathological changes are due to massive invasion of red cells and cells of the reticulo-endothelium by *Bartonella bacilliformis*. There is a severe anaemia, and marked reticulo-endothelial proliferation The skin of patients dying during Oroya fever is wax-like; there may be diffuse or punctate haemorrhages in the mucosae and subcutaneous tissues There are haemorrhagic petechiae in the serous membranes and internal organs The lymph glands, the spleen and the liver are enlarged The bone marrow is unusually soft and shows a greyish-red mottling On histo-

endothelial cells, some

thin layer of shiny skin. In addition to these miliary lesions rather comparable nodules can be felt in the deeper layers of the skin, these grow in size, attain a diameter of some centimetres, and protrude above the surface of the skin They may or may not break through the skin surface; in the former event they take the form of red tumours of irregular contour, which may become pedunculated These latter lesions bleed particularly easily, and usually they become secondarily infected They have been called the 'mulaire' type of verrugas.

The various types of lesions, the miliary, the nodular and the mulaire, all appear concurrently in successive crops Their numbers may be [illegible]

as 2 years The lesions then heal without scar formation, unless they have been the seat of gross secondary infection

DIAGNOSIS

The clinical pictures of Oroya fever and of verruga peruana, in relation to the area from which the patient comes, usually are characteristic In the non-eruptive Oroya fever stage the diagnosis rapidly can be confirmed by microscopical examination of blood films for the organism, which usually can be seen in great numbers of the red cells In the verrugous or eruptive stage biopsy of the lesions will reveal their presence in rather smaller numbers in the endothelial cells

TREATMENT

There is no evidence that any drug acts specifically on the *Bartonella* infection The anaemia of the Oroya fever stage, while it progresses, may be controlled by suitable blood transfusions

What is important in view of the extreme risk of a fulminating *Salmonella* infection is the prevention of this Chloramphenicol is the most effective drug for this purpose; it should be given promptly on diagnosis in every case of Oroya fever Its use has been followed by a marked fall in the mortality previously associated with the disease

The fever is intermittent or remittent; it rises two to four degrees Fahrenheit in the evenings and falls again in the mornings. The duration of the fever and other accompanying acute symptoms in favourable cases is from two to six weeks; they then slowly diminish and disappear. Septicaemic complications are common; sometimes the patient dies as a result of them during the Oroya fever by the tenth day, but more commonly he does so between the third and sixth weeks of illness. It is now established that the principal cause of mortality is a particular susceptibility of these patients to septicaemic infection with *Salmonella* organisms, commonly *Sal. typhimurium*, of animal origin. This may occur during the stage of massive red cell destruction; usually it occurs in convalescence during regeneration of the red cells with a

may be over 90 per cent.

Early in the Oroya fever stage of the disease a severe rapidly progressive anaemia becomes clinically evident. The blood volume is diminished; the sedimentation rate is much increased. The white cell count is not significantly affected. The red cell count markedly falls, often to one million, the rate of the fall being up to half a million in 24 hours. The red cell diameters, volume and thickness all are increased, the colour index usually is low; there is a rise in the reticulocyte count,

bacilliformis is present usually in great numbers in the blood throughout the Oroya fever stage of the disease, in very severe cases almost every red cell is infected, often with many organisms. The decline in the numbers and the eventual disappearance of the causative organisms from the red cells commonly, though not invariably, are associated with a consonant diminution and arrest of the progress of the anaemia.

Verruga peruana. While verruga peruana commonly follows as a sequel of a recognized attack of Oroya fever, the attack of the latter may have been one of abnormal mildness and the patient indeed may

such extraneous circumstances has not been assessed What appears to be much more important is the character of exposure to falciparum malaria The native inhabitant who has been repeatedly reinfected for years does not develop blackwater fever so long as he is left undisturbed in his malarial environment Experience in World War II, however, demonstrated clearly that if the transmission amongst the community were reduced by incomplete entomological control, or if individuals were incompletely protected against the disease by drugs, blackwater fever appeared It is believed that this was largely due to the creation of some state of sensitivity resulting from partial loss of hard-earned immunity, which led to sharp haemolysis upon successful reinfection with falciparum, especially the homologous strain

It seems probable that some similar mechanism may be involved in the appearance of the disease in visitors and may explain the fact that it occurs as a rule only after months in the endemic area

Irregular therapeutic and suppressive dosage of anti-malarial drugs, nearly always quinine, is an important factor in many cases The habit of taking quinine irregularly, particularly at times of 'fever', is a very common prelude to blackwater Moreover, before the introduction of modern drugs, blackwater frequently appeared in cases of falciparum malaria undergoing quinine therapy

There is plenty of evidence indicating that the role of quinine in initiating lysis is a direct one but it is possible that the drug, because of its general inefficiency as a suppressive, may sometimes foster the development of a sensitivity state in the individual patient resembling that which appears in the incompletely protected native Possibly both processes may be involved in some individuals

PATHOLOGY

Pathogenesis The essential feature of blackwater is the intravascular haemolysis, the pathogenesis of which is not understood No haemolytic strain of falciparum parasite has ever been identified There is no evidence of a specific circulating haemolysin The saline fragility of the red cells in an active case is not increased There are various theories concerning the origin of haemolysis, none of which has been confirmed It has been suggested that the lysis is merely an uninhibited exacerbation of normal haemolytic processes or that the parasites contain a substance resembling the Rh factor which leads to autoimmunization and lysis The most attractive hypothesis proposes that the parasite changes the chemical composition of the individual red cell, rendering it autoantigenic and so capable of stimulating the production of autoantibodies which, together with the 'sensitized' erythrocytes and complement, precipitate lysis

VI

BLACKWATER FEVER

DEFINITION

A SERIOUS state of acute haemolysis accompanied by haemoglobinuria and associated with a history of present or past malaria

GEOGRAPHICAL DISTRIBUTION

Blackwater fever appears irregularly within endemic and hyperendemic malarial regions It does not occur outside the distribution of malaria except in individuals who have been infected elsewhere

AETIOLOGY

It is now largely agreed that malaria in some unexplained manner is responsible for the haemolysis

Blackwater fever appears almost exclusively in falciparum endemic areas Other forms of malaria are very rarely, if ever, involved. Falciparum parasites are present in the peripheral blood in about half the cases on first examination, they are usually absent in advanced cases but often appear or reappear in early convalescence Blackwater fever may develop during the course of an overt falciparum attack.

The patient usually has a history of repeated clinical attacks of malaria over a period of months or even years, often incorrectly and inadequately treated with antimalarial drugs, especially quinine

The syndrome occurs most commonly in visitors after some months or more exposure in an endemic area, and usually after repeated attacks of malaria It may occasionally develop after only a few weeks or even during the first attack of malaria in fresh arrivals

It appears also in a very small proportion of the native population, mainly in children or in those who live under conditions of incomplete protection against malaria and are no longer fully exposed to the chances of frequent infection shared by the general population It rarely appears in infants.

There is no racial immunity Given the right conditions negroes are as susceptible as Europeans or Asiatics The sexes are equally affected under the same conditions.

[illegible]

cases arising in a single town or even the same house. The true value of

The parasite is almost always *P falciparum* Sometimes there may be mixed infections

Leucocytes There are no characteristic changes Leucocytosis may be present early, but it is commoner to find a mild leucopenia with a relative increase in lymphocytes, and sometimes an absolute increase in monocytes

Chemical changes The biochemical composition of the blood largely depends on the physical state of the patient

During active lysis haemoglobin and methaemalbumin are present in low concentration in the plasma The latter pigment is formed by the combination of haematin (apparently split from the haemoglobin liberated into the plasma) and crystalbumin, it does not pass into the urine The pigments within the erythrocytes are apparently unchanged, there is no intracellular or extracellular formation of methaemoglobin

The blood urea nitrogen concentration is raised slightly in practically all cases, irrespective of the existence of renal insufficiency When the renal syndrome with oliguria or anuria has developed the blood urea nitrogen rises to great heights (400 mgm per 100 ml or higher) as in other forms of acute uraemia After recovery from renal failure it gradually returns to normal

Plasma protein concentration is often low, the reduction being mainly in albumin There is sometimes an accompanying increase in globulin

Plasma bilirubin is raised, especially in cases showing obvious hepatic dysfunction The indirect van den Bergh reaction is strongly positive, in severe cases there may be direct and biphasic positive reactions

Whole blood and plasma chlorides are low in cases presenting with dehydration or severe vomiting

The carbon-dioxide combining power of the plasma may be considerably reduced in some cases, unaltered in others equally severe There is no clear evidence of any changes in blood pH towards acidosis, but this is indicated in some cases in which the lowered CO_2 combining power is associated with changes in plasma phosphate

The Urine The appearance of the urine during the syndrome is described in the section dealing with the clinical picture

The urine is unconcentrated The chloride and urea concentrations are both reduced, owing to renal tubular insufficiency This failure to concentrate urine is pronounced during lysis and continues for some time into convalescence After recovery from anuria large quantities of dilute urine are passed for some days

The measurement of specific gravity must not be taken as a guide to urinary concentration, chemical analysis is necessary High specific gravity may be a feature of poorly concentrated urine containing pigment or albumin

(In a few cases there may be clinical cardiac failure, but death in blackwater fever results most commonly from renal failure, vascular collapse or hepatic failure. The heart muscle may show some change including granular fatty degeneration, fragmentation and loss of stria- [illegible]

[illegible] malaria and are discussed elsewhere (p. 193) In cases complicated by vascular collapse, the autopsy findings are those of shock.

Renal failure is the commonest fatal accident It was at one time believed that the anuria arose from 'blockage' of the renal tubules by haemoglobin pigments precipitated in an acid urine. This theory demanded the presence of haemoglobin, an acid urine and a high urinary concentration of salt. Recent observation has shown that anuria may develop when the urine is free from pigment and when it is alkaline or neutral Moreover, the concentration of salt in the urine in blackwater fever is invariably low because of the prevailing damage to the tubular epithelium (The modern view is that the changes arise from [illegible]

LABORATORY FINDINGS

The Blood The haemolysis leads to anaemia, which develops rapidly and is often severe The red cell count may fall as low as one million or fewer cells per cu mm, sometimes *even after the first haemolysis By the* time the patient is first seen it usually lies between two and three million cells per cu mm

During vascular collapse the loss of plasma fluid leads to haemoconcentration in which the red cell count and haemoglobin concentration rise roughly in proportion to the loss of circulating fluid It may [illegible]

patient

Erythrocytes No obvious changes in the size or shape of erythrocytes occur Reticulocyte numbers vary widely within normal limits The cellular haemoglobin concentration is normal

Parasites: Plasmodia are present in about 50 per cent of cases in the early stages of haemolysis As haemolysis proceeds they frequently disappear If antimalarial treatment has not been given they are likely to reappear in early convalescence

During haemolysis the red cell count falls rapidly, one or two million or more cells per cu mm may be lost in the course of a few hours (See section on PATHOLOGY)

THE URINE

Haemoglobin appears in the urine shortly after the commencement of haemolysis and persists for a time after haemolysis has stopped From the clinical point of view, however, haemolysis and haemoglobinuria are usually considered roughly contemporaneous During [illegible]

methaemoglobin dark brown The colour of any given specimen depends on which pigment predominates Oxyhaemoglobin is in excess in alkaline urine, methaemoglobin in acid

The first specimen of urine passed after haemolysis is often the darkest, it is usually dark red or almost black Occasionally the pigments may appear more gradually, the urine colouring deeper over the course of a few hours

As the lysis abates each specimen of urine becomes successively less pigmented until finally clear During succeeding haemolytic phases the pigments return to the urine

Albumin is present in high concentration throughout the lytic period When the pigment clears, the albumin usually goes with it The urine of the interlytic phase is thus non-pigmented and practically free from albumin

During haemoglobinuria there is always a thick greyish brown deposit in the urine containing hyaline and granular casts, amorphous epithelial debris and haemoglobin pigments This deposit becomes very much reduced as the urine becomes clear Casts persist in considerable numbers, however, for some time after the pigment has been lost

The urine passed during and for some days subsequent to haemolysis is unconcentrated so far as its electrolyte concentration is concerned, although its specific gravity may be high as a result of its protein content

Reaction The urine passed during haemolysis may be acid, neutral or alkaline

Volume In some mild cases there may be continuous polyuria even during haemolysis and in convalescence In such cases the urine is unconcentrated and the picture is that of tubular insufficiency

In the majority of cases, however, there is some oliguria Subjects in whom anuria subsequently appears are usually oliguric from the start The anuria is seldom absolute, commonly a few ounces may be passed in the day If anuria develops during a lytic phase the small amount of

CLINICAL PICTURE

Most patients with blackwater fever have a history of exposure in an endemic or hyperendemic falciparum area lasting for several months or longer Occasionally the syndrome may develop within a few weeks of entering the endemic area There is usually a history of repeated attacks of falciparum malaria of varying severity, interspersed with persistent general malaise, headache and backache, but cases do occur in which there is no evidence of any previous clinical malaria

Blackwater fever sometimes occurs in individuals who have never taken antimalarial drugs, but it is common to find that the patient has been taking suppressive quinine therapy irregularly or has been treating himself for malarial attacks with occasional heavy doses of quinine It may appear during the first two days of quinine therapy in otherwise uncomplicated falciparum malaria It is rare following suppression or therapy by other antimalarial drugs.

The patient may occasionally have had one or more previous attacks of blackwater fever

The onset of haemoglobinuria is usually sudden It may appear without incident during a falciparum attack or during apparent health Sometimes the patient mentions its appearance quite casually.

In most cases there is a short prodromal period lasting two or three days, during which there is malaise, headache, backache and sometimes slight fever The onset of the syndrome is proclaimed by a sudden rise in temperature which reaches 103° to 105° F in the course of a few hours Severe rigor is common The first specimen of pigmented urine is commonly passed during or immediately after the initial rigor The temperature may become intermittent, subsiding rapidly only to rise again with further rigor, with heavy sweating between each exacerbation of fever More commonly it becomes remittent, varying between 102° and 104° F In a few cases the temperature may continue to rise, sweating ceases, and hyperpyrexia develops Some mild cases and others in which shock develops early may be practically afebrile throughout The onset of shock in all cases is followed by a dramatic fall in temperature Except where the temperature is very high the skin is moist throughout In cases with intermittent fever sweating may be profuse when the temperature falls, but, unlike malaria, the fall of temperature and accompanying sweating do not lead to any sense of well-being

Haemolysis may occur only once during the syndrome or may recur

frequently mild

inelastic, pale and moist The blood pressures fall; the diastolic is often not measurable The plasma volume falls rapidly with accompanying haemoconcentration which may mask the anaemia The patient collapses and dies of vascular failure

If the shocked patient survives for some time petechial haemorrhages may appear in the skin and mucous membranes and the vomitus and faeces may both contain altered blood

The severe vomiting, watery diarrhoea and sweating commonly lead to an appreciable degree of dehydration which, in the absence of shock, is indicated by the stretched inelastic skin, prominent malar bones and general parched appearance of the patient, and by the disappearance or reduction of chloride from the already dilute urine and sometimes, but not always, by falling blood chlorides Dehydration may be masked by the symptoms of shock

COURSE AND PROGNOSIS

Blackwater fever may be mild, most cases are severe, they may occasionally be fulminating At any stage even in the apparently mild case fatal complications may develop

The length of the illness varies from a few days to several weeks The number of lytic episodes cannot be predicted In cases with multiple haemolyses the interlytic period may extend for anything from a few hours to more than a week The initial haemolysis is usually the most severe

In the uncomplicated case recovery is rapid and convalescence uneventful Malaria may appear in early convalescence and requires treatment

Complications are frequently fatal Their appearance calls for a very grave prognosis More than half the deaths arise from renal failure, most of the others from vascular failure, hepatic insufficiency or uncontrollable lysis Occasionally there may be true cardiac failure, sometimes occurring during apparently satisfactory convalescence

The mortality rate varies from 20 to 30 per cent of all cases

Because of the risks of further attacks of blackwater fever, the individual should be advised to leave the region in which the attack occurred Some have survived several attacks, but there is little point in exposing the patient to further risk unless it is essential If he must return to the tropics it is advisable for him to return to an area other than that in which he developed blackwater, and to take the utmost precautions against further attacks of falciparum malaria

DIAGNOSIS

Haemoglobinuria and increasing anaemia in a patient exposed to falciparum infection should be diagnosed as blackwater fever The possibility of sickle-cell crises must be excluded in Africans

urine passed is often thick black tarry material loaded with albumin and debris

Renal failure Tubular dysfunction evidenced by the passage of poorly concentrated urine occurs probably in every case At any time, however, a much more serious form of renal failure may arise in which there is gross reduction of urinary flow amounting to suppression of urine. This is the most dreaded of all complications of blackwater fever and accounts for more than half the deaths Its appearance is independent of the urinary reaction at the time of the passage of pigments; it may occur in the post-lytic as well as the lytic phase Anuria develops suddenly and its onset may be missed unless the volume of each specimen passed is measured separately. There may be no clinical indication of the onset of anuria other than the fall in urinary volume, although in some cases there may be severe backache and pains in the loins Once anuria has appeared recovery is rare The patient proceeds into acute uraemia, with rising blood urea nitrogen, sometimes increasing systolic blood pressure, oedema and often coma Recovery occasionally takes place even when the anuria has persisted for days; it is accompanied by a few days of polyuria associated with the passage of dilute urine

The renal failure syndrome (renal anoxia) may develop during or independent of vascular collapse.

Hepatic insufficiency Practically all cases show signs of hepatic dysfunction soon after the onset The degree of liver involvement varies considerably from case to case There is increasing epigastric discomfort, distension, nausea and often severe vomiting The vomitus is watery and bilious in the early stages; in collapsed patients it may contain altered blood The liver edge becomes palpable and tender The enlargement may proceed rapidly until the edge presents several fingers breadth below the costal margin Jaundice is often visible by the end of the first day It deepens fast in serious cases Bilirubin appears in the urine, and may be masked by the blood pigments The faeces are watery and often contain bile There is sometimes severe watery diarrhoea In cases in which the hepatic involvement is severe the vomiting may be intractable and accompanied by hiccup Sometimes the liver failure may advance so rapidly as to dominate the picture and suggest acute infective hepatitis

General In the early stages the patient is fully conscious, restless and anxious over his condition In the terminal stages he is often deeply comatose and incontinent; occasionally he is still conscious

Prostration is severe from the first, and its severity often bears no relation to the fever

Shock and dehydration In severe cases and occasionally in apparently mild ones, medical shock may develop. The patient becomes increasingly restless, his face is drawn, the eyes look sunken, the skin is

An attempt must be made to keep a balance between the fluid intake and the output (estimated as urine, faeces, sweat and vomit) Excessive infusion of fluid may precipitate disaster

Blood transfusion If the erythrocyte count falls to 2 0 million or fewer cells per cu mm, or if the haemolysis is proceeding very rapidly, transfusion is necessary

Citrated blood is given, and the amount injected must be included in the fluid intake for the day

Because of the likelihood of disturbances of plasma agglutinin pattern, transfusion is often a difficult affair in blackwater fever as it is in malaria *It is essential to cross-match the donor's cells and the recipient's serum and vice versa*

The purpose of transfusion is to restore the numbers of red cells and so ensure the carriage of oxygen to the tissues It must not be pushed too far It is seldom necessary to give more than two pints in one day

Renal failure Heavy alkalinization such as was formerly advised, serves no useful purpose and may be harmful It should be abandoned

Diuretics are useless once anuria has developed

The patient with anuria and rising blood urea should be put on a protein-sparing diet Protein as such is temporarily withheld and introduced gradually in convalescence (starting with 40 to 50 gm a day) A dose of 100 to 300 gm glucose or lactose in 600 ml of water is given orally or by stomach tube, or, if necessary, by vein or by polythene tube into the vena cava Heparin, 500 units, may be added to the fluid if given intravenously, in order to avoid clotting Salt/water dehydration must be treated in the usual way by intravenous infusion of isotonic saline Care must be taken to avoid waterlogging An input output fluid account must be kept If there is any considerable elevation of serum potassium, 20 units of soluble insulin may be given subcutaneously for every 50 gm glucose administered Sodium charged cation exchange resin may also be given orally in doses of 15 gm three times a day Treatment must be controlled by measurements of serum electrolyte concentrations

Under suitable conditions dialysis of the blood in the so-called artificial kidney might conceivably be effective Local injection of the renal pedicles with novocain and even spinal anaesthesia have been used in similar syndromes in an attempt to break the reflex arc which is believed to bring about the changes in the renal blood flow

Vomiting or hiccup may be relieved by sucking ice or by morphia The latter may be used for the restless patient

Other methods of therapy for which equivocal success can be claimed are barbiturates, snake antivenin and vitamin C in large doses

The patient should be given light foods if he will take them Glucose should be added to all drinks and if necessary, to infusions

Causes of haemoglobinuria other than blackwater fever may have to be excluded Haemolysis may be induced in some subjects by quinine in the absence of malaria Such haemolysis is mild and unaccompanied by serious symptoms It can be induced regularly by the administration of the drug and there may be some history of this or it may be possible to determine the sensitivity subsequent to the attack of blackwater. To do so it is necessary to make sure that any underlying falciparum malaria has been radically cured since it has been shown that quinine may precipitate lysis in a patient when falciparum malaria is present and fail to do so after the disease has been cured. In patients of negroid descent a syndrome of haemoglobinuria and oliguria may be precipitated by the administration of an 8-amino-quinoline. (See page 215).

Careful inquiry into the patient's history should help to differentiate

nuria The presence of erythrocytes rather than haemoglobin pigments in the urine determines the diagnosis of haematuria

The signs of liver dysfunction in blackwater fever may closely resemble those of infective hepatitis or Weil's disease, but the history of the case should make identification easy

The recognition of renal failure is very important in blackwater fever Every specimen of urine passed should be examined separately and its volume measured and recorded

The absence of malaria parasites from the peripheral blood has no diagnostic significance

TREATMENT

If parasites cannot be found suppressive therapy should be continued in individuals already taking drugs. A full course of antimalarial treatment should be begun in early convalescence even in the absence of parasites

Vascular failure: The patient should be moved as little as possible In the field it is better to nurse him where he is if the alternative is a rough passage into hospital

Treatment of vascular failure in blackwater is the same as in other conditions The blood volume must be restored by plasma in the first instance followed if necessary by saline or glucose infusion

Dehydration Excessive sweating, diarrhoea or vomiting may lead to severe loss of fluid and salt

In mild cases these may be replaced orally. In most cases it will be necessary to replace them by intravenous infusion.

especially native children, there may be dozens of chigoes in the feet, the thighs, the perinaeum and external genitalia In adults, especially Europeans, the numbers usually are less, and commonly there are only a few in the feet alone.

The first symptom is itching, later there is inflammation and swelling, later still ulceration, and finally possibly gross sepsis

TREATMENT

The pregnant female should be eased out with a sterile needle, and the wound cleaned and dressed If this is done early, and the flea is not ruptured in the process, the small lesion soon heals Secondary sepsis is the main source of trouble, the aim is to avoid this

PROPHYLAXIS

The bare skin should never be allowed to come into contact with the floor Shoes should always be worn Cleanliness in the home is of obvious importance Insecticidal treatment of the floor may help

VII

THE CHIGOE FLEA

DEFINITION

TUNGA PENETRANS, the chigoe or jigger, is a flea both sexes of which feed on warm-blooded animals The pregnant female buries her head, thorax and abdomen in the skin, where she stays until she oviposits. Commonly she infests the feet causing discomfort and even lameness and often, as a result of her presence, secondary sepsis

GEOGRAPHICAL DISTRIBUTION

Originating in South America, the chigoe has been conveyed to most parts of the world. It has established itself in many parts of the tropics, and from some of these points has steadily extended its range throughout neighbouring territories It now occurs extensively over tropical Africa; but although it must repeatedly have been introduced into India and the Far East it has not spread there

AETIOLOGY

The adults of both sexes of *Tunga penetrans* live in dust or sand around or in huts and houses They take blood meals from any warm-blooded animal or bird After fertilization the female chigoe attaches herself and bores, head first, into the soft epidermis of man and some other animals, especially the pig, until her head lies in the dermis and the posterior end of her abdomen is just beneath the skin surface. For over a week her abdomen steadily hypertrophies until it is about the size of a small pea, this is largely a physiological development, but in part it is due to distension with blood and the developing ovaries and eggs The eggs are then extruded through the posterior abdominal aperture to the exterior, 150 to 200 escape at intervals, in lots of up to 10 eggs at a time, over 7 to 10 days, the flea after this shrinks and dies *in situ* A larva emerges from each egg three or four days after its deposition; this lives in dust, undergoes two moults, and pupates, an imago then emerges This developmental cycle occupies about seventeen days.

CLINICAL PICTURE

The sites most frequently attacked are the spaces between the toes, under and around the toe nails, and the soles of the feet especially the instep, occasionally other parts of the body are infested In children,

of the intestinal wall and is never found in the blood stream or in the urine In the clinical attack it is present in enormous numbers in the faeces and vomitus

In most cases the vibrio may be found in the faeces and vomitus for about five days only. *Occasionally it may persist for as long as a few* weeks There are no true 'carriers' of the disease in whom the infection persists for long periods

It appears, therefore, that the maintenance of endemicity in a given area must depend on the direct spread of infection from case to case, the mode of transmission being mainly through faeces Individuals may become infected without showing any clinical evidence of the disease It is thus not necessary to have overt cases for transmission to occur

The organism can survive on moist clothing for up to three days It dies rapidly in pure water but survives for days (maximum of 6 weeks) in slightly dirty water containing salts and organic matter It is easily killed by moderate heat (55° C for half an hour) and acid

In a community the infection spreads most commonly through infected water (including ice and cold drinks) contaminated with faeces Other potable fluids including milk, cold cooked foods, vegetables sprinkled with water and uncooked fruits may also be concerned with the spread of infection

Spread may occur from case to case through direct contact with faeces or vomitus

The only important living agent of transmission is the domestic fly

In endemic areas most cases occur in the hot moist season, possibly because of the mechanical flushing of local filthy water supplies Thus, the incidence is highest in Bengal in the early rains (May, June and July) and lowest in the dry weather

Epidemics arise from the introduction of the vibrio by infected individuals, who may or may not show clinical signs of infection Once the disease is introduced it spreads by the same means as in the endemic area Where sanitary conditions are good there is little chance of spread Where they are so bad that water supplies can be continually infected, cholera becomes rapidly established Since the individual case is usually infective for only a few days the extension of the disease *from endemic areas is largely limited by the rate of travel* Modern transport is a potential threat to insanitary areas outside the endemic foci, and rigid international control is necessary to keep the disease confined

In non-endemic areas prevention of the import of the disease is a matter of sanitary control and quarantine of ships and aircraft from infected areas and the isolation of suspected cases Where cholera has appeared local water supplies must be examined and protected from pollution Chlorination will rapidly destroy the vibrio. Individual

VIII

CHOLERA

DEFINITION

CHOLERA is an acute, self-limiting, often fatal, infectious disease of short duration caused by a specific organism *Vibrio cholerae*, which multiplies in the gut contents but does not invade the blood stream or tissues It is characterized by copious watery diarrhoea, vomiting, muscle cramps, severe dehydration, vascular collapse and various complications especially suppression of urine and acute uraemia

GEOGRAPHICAL DISTRIBUTION

Cholera has a strictly endemic distribution in certain tropical regions of high humidity and temperature, especially Bengal and Madras in India Other foci have occurred in China, Burma and the Phillipines The most important endemic focus is that in Bengal, which is confined mainly to districts along the river Hooghly.

Local epidemic or pandemic extensions of the disease have occurred from time to time along trade routes and other lines of communication

AETIOLOGY

shaped and motile It is Gram-negative and grows easily at 37° C in ordinary bacteriological media Vibrios are divided into groups depending upon their antigenic pattern Those known to cause cholera have a common H antigen and specific O antigens There are three principal strains, i e the Inaba, Ogawa and Hikojima One of these

In nature the organism is pathogenic only to man. Other animals are not infected. A condition somewhat resembling cholera can, however, be induced by artificial gut infection of young guinea pigs and rabbits

In the human case the vibrio grows and multiplies almost entirely in the lumen of the gut It does not penetrate beyond the submucosa

PATHOLOGY

Pathogenesis In cholera the organisms remain in the gut and do not invade the blood stream In the gut the vibrios multiply rapidly and cause the loss of enormous quantities of water and salt from the tissues through the intestinal epithelium into the lumen and so outside the body This is the basic physiological lesion Certain local effects on the gut wall may be produced There is often considerable shredding of the epithelium and in the later stages some bleeding into the lumen There is never any deep ulceration of the intestinal wall

The mode of action of the infection is not understood No soluble toxin has been identified It has been shown, however, that poisonous substances or endotoxins are formed *in vitro* during the growth and lysis of the vibrio, and it may be that these are involved The endotoxin has been shown in animals to affect the permeability of the gut wall to electrolytes Its effect can be neutralized to some extent by antibodies derived from injection of killed cultures of cholera vibrios It is probable that the whole syndrome arises as a result of the action of a vibrio or its products such as this 'endotoxin' on the physiological permeability of the intestinal wall

The loss of fluid and electrolytes is rapid and severe A state of mixed salt and water dehydration is quickly achieved. Some degree of acidosis and haemoconcentration results

The serious dehydration itself affects the circulating plasma volume, which is often further reduced by the appearance of vascular collapse Haemoconcentration is therefore pronounced in severe cases, there is an equivalent increase in haemoglobin concentration The viscosity of the blood increases considerably and the efficiency of the circulation is correspondingly diminished The combination of dehydration and shock brings about functional and structural tissue damage particularly in the kidney

Morbid Anatomy The information regarding the morbid anatomy of cholera [illegible]

Rigor mortis develops rapidly The muscles are deep red and dehydrated, violent post-mortem contractions may occur The tissues are dry The blood is viscid There may be scattered petechial haemorrhages in the mucous membrane of the intestine and in the pericardium

Changes in the organs are commoner in cases which have survived to the late stages before death The anuric and uraemic case may present kidney lesions similar to those often met in other examples of the renal anoxia syndrome There may be irregular ischaemia of the cortex involving the glomeruli in a patchy manner, some medullary congestion and epithelial degeneration and desquamation, particularly in the

drinking and washing supplies should be boiled or chlorinated before use, and the strictest attention must be paid to the preparation and consumption of food

Anti-fly precautions should be enforced.

Individual or mass protection by the use of vaccines of dead vibrios, preferably local strains, should be carried out if possible. Individual injection is given in two doses (first dose 0.5 ml and second dose 1 0 ml) a week apart When vaccination is used for mass protection, for example, during an epidemic, a single dose of 1.0 ml is employed.[1]

Modern vaccines do not usually produce a febrile reaction They endow some immunity which is effective for 4 to 6 months Repeated vaccination is necessary in individuals residing for longer periods in infected areas

Resistance to infection In a group of individuals exposed to the same source of infection by no means all may become infected Of those infected some will show the fully developed syndrome, others may have no clinical ill effects It is believed that certain individuals may thus present some natural resistance to infection The acidity of the gastric juice may act as a barrier to infection of the gut, the vibrios being highly susceptible to an acid environment, reduction in gastric acidity may predispose to infection

Newcomers to the endemic area are believed to be more likely to become infected, but this is not certain There is little evidence of herd immunity in the sense that it exists in malaria, the local population of an endemic area may be highly susceptible during outbreaks.

The cholera outbreak in a community is self limited It tends to die out after reaching its peak This may be in some measure due to the large number of subclinical cases which develop or to the acquisition of temporary individual immunity. It has been demonstrated, however, that one attack does not protect against subsequent infection, except partially for a very limited period.

In epidemics a smaller proportion of the local population may be infected than might be anticipated Napier, for instance, has pointed out the striking difference between the infection rate of cholera (about one in three) and smallpox, in an exposed community in which there is free intercommunication

Antibodies, including agglutinins, and some measure of protection against infection are produced in animals by the inoculaton of killed vibrio cultures intramuscularly or subcutaneously Such inoculations may afford considerable protection in man

Race, sex and age appear to play little part in the incidence of the disease. Malnutrition and poor health probably predispose to infection, but otherwise healthy subjects are often readily infected

[1] Vaccine is standardized to contain 8000 million organisms per 1 0 ml

the infection has been so severe that death has resulted before the classical watery diarrhoea has become established On the other hand, infections of the intestinal contents may be present without causing any clinical signs In epidemics the early and late cases are often less severe than those at the height of the outbreak

The majority of the clinically overt cases are severe Nevertheless, the condition is of short duration, seldom lasting more than five days

Incubation Period The incubation period varies from a few hours to five days Commonly it is about three days There are no prodromal symptoms

The Classical Attack It is usual to describe the development of a severe case in three stages, which often merge indistinguishably into one another These stages are those of (i) evacuation, (ii) collapse and (iii) reaction

The stage of evacuation commences with diarrhoea which may at first be mild, but which soon empties the bowel of faeces and changes to the urgent watery diarrhoea of the classical condition The patient now passes frequent watery stools which amount to little more than

vibrios In the late stages there may be a little blood

Bowel motions are frequent, effortless and uncontrolled Napier refers

no colic and the patient is often scarcely aware that he is evacuating his bowel Contamination of bed clothing is therefore frequent unless watched for

Vomiting begins as a rule shortly after the diarrhoea has started There is no nausea The patient has little or no control over the vomitus which gushes out with considerable force and volume The watery vomit is essentially similar in appearance and content to the stool and like the latter contains enormous numbers of vibrios and is highly infective It constitutes a real danger to the unwary physician

Evacuation continues for a variable time and frequently persists into the second stage of the disease, that of collapse This algid state may be reached in a few hours in acute cases in one or more days in less severe attacks Evacuation seldom continues, however for more than three days The frequent bowel evacuation and vomiting lead rapidly to tremendous loss of fluid and electrolytes Within a matter of hours the severely ill patient becomes dehydrated The whole body seems to shrink, subcutaneous fluid is lost and the pale clammy skin becomes

cortical tubules, which, together with the collecting tubules may contain casts of albuminous material and epithelial debris. On the other hand, there may be little evidence of structural change in the kidneys of the anuric case, especially if death has occurred soon after the renal failure. The liver may be congested and show some degenerative lesions, mainly centrilobular The gall bladder and bile ducts are filled with dark viscid inspissated bile.

Pulmonary oedema may be present in shocked cases. Otherwise the lungs are shrunken and anaemic.

CLINICAL PATHOLOGY

In the fully developed case the stools are watery, of very low specific gravity and contain shed epithelium and mucus As much as 15 litres of this transudate may be lost in 24 hours The total sodium chloride loss may be as great as 30 gm The stool is invariably alkaline.

Blood Cells The dehydration and loss of plasma volume cause rapid haemoconcentration In severe cases the blood is viscid, and the erythrocyte count may become as high as 8 or 9 million cells per cu mm The white cell count is correspondingly increased

Blood The viscosity and specific gravity is increased roughly in proportion to the loss of plasma volume The specific gravity of normal blood measured by the method described in the section on treatment is about 1054. In severe cases at the height of 'fluid loss' it may be 1060 or even more

The chemical constituents of the blood depend primarily upon the state of hydration and the successful function or otherwise of the kidneys.

In the severe case the total chloride concentration is low, the sodium is lower in proportion, the potassium is usually unchanged.

The blood urea N concentration is raised above the normal range in most cases. In the anuric case it rises steadily to reach very high figures In recovery after anuria it falls rapidly

Plasma protein concentration is raised considerably in the dehydrated case.

Urine The output is low. There may be no urinary secretion The specific gravity may be high and the urine deeply pigmented Nevertheless, the urea and electrolyte content is low and there may be no

[illegible]

CLINICAL PICTURE

Cholera may be mild or severe. Cases have been described in which

no circulatory recovery or a temporary reaction stage may be followed by serious and sometimes irreversible changes in vital organ function, and the threat to life again becomes urgent

This is particularly so in cases in which anuria has developed If the anuria has been of very short duration reaction may be immediately followed by recovery of urinary flow and renal function On the other hand, however, in some cases, especially those in which the anuria has been prolonged, renal failure may persist into acute uraemia Such cases usually die within a few days, even in their late stages, however, recovery may occur, as it does in other examples of the renal anoxia syndrome Occasionally, the anuria of the collapse may be followed by a short period of oliguria in which small volumes of urine containing albumin and casts may be passed, anuria then reappears and the patient dies in uraemia

In some cases after brief improvement, the peripheral circulation may fail again and the patient dies of shock It must be noted that in many fatal cases, the algid stage persists to death and there is no recovery stage at all

The whole progress of the cholera case is only a matter of a few days at the most Recovery when it occurs is usually rapid, especially with correct treatment when it is often remarkable, the dehydrated corpse-like patient visibly swelling into something resembling normality almost while he is being watched

COURSE AND PROGNOSIS

[illegible]

circulatory failure or both The very severe case may perish in a few hours This is especially so in children

Prognosis depends considerably on the length of time elapsing from onset to commencement of treatment If dehydration is very severe and shock develops, the outlook is bad The longer the dehydrated patient is left untreated, the worse the prognosis Prognosis is bad if anuria has already developed and persisted for some hours before treatment.

The recovery rate is high with efficient treatment, except in advanced and shocked patients

Complications of cholera other than renal failure and shock, are rare Pneumonia is sometimes described, especially in outbreaks in cold climates, and gangrene of the extremities has been reported in a few neglected cases There are no sequelae in the recovered case Once the tissue water-salt balance and plasma volume have been adjusted, return to normal is very fast, usually a matter of a few days

The death rate in local outbreaks or in epidemics is very high, often

inelastic and stretched over the underlying tissues. The eyes are sunken, the cheeks hollow, the skin tight over the malar prominences The mouth and tongue are dry; there is extreme thirst; the voice is husky. The patient becomes anxious, foreboding and restless but remains mentally clear As the dehydration continues, the circulation becomes inefficient The blood pressures fall, the pulse quickens and may be impalpable at the wrist The picture now becomes essentially one of dehydration and vascular collapse and closely resembles similar conditions such as severe heat exhaustion in which medical shock has developed

Muscle cramps are common once dehydration has become established They are severe and painful, frequent, of short duration, and arise particularly in the legs The abdominal muscles are affected only in the later stages.

The rectal temperature is seldom raised above normal Skin and oral temperatures are often subnormal

At the start of the syndrome, the urine volume is reduced and there is usually a thin cloud of albumin, as the dehydration proceeds, the urinary output diminishes Even in relatively mild cases there is oliguria. In severe cases there may be complete urinary suppression which may be only temporary or may pass on to irreversible acute uraemia The urine has a low electrolyte concentration It contains albumin and granular tubular casts and may have high specific gravity and pigment

By the time dehydration is manifest the plasma volume is considerably reduced from this alone When vascular collapse supervenes there is a further reduction The result is an extreme loss of plasma volume which may amount to over half the initial volume and a corresponding concentration of the cellular elements of the blood. The red cell count and haemoglobin concentration rise steadily to a maximum which may be greatly in excess of normal The viscosity of the blood is increased.

Death is common at this point from the combined effects of dehydration and shock

The fate of the patient is determined to a considerable extent by the degree and duration of evacuation and collapse. If the algid state has lasted only a few hours, the third stage, that of circulatory recovery, is commonly followed by rapid return to health Reaction is ushered in by a rise of blood pressure, slowing and improvement of volume of the pulse, a return of normal coloration to the skin and a rise of body

If the algid stage has been prolonged [illegible] may be

has no ill effects It thus appears to be perfectly safe to use either solution.

Not more than two pints of hypertonic saline should be given in succession Thereafter further infusions should be administered as isotonic saline or mixtures of isotonic saline and 5 per cent glucose

The following details are modified from those followed in the Campbell Hospital in Calcutta

Solutions.

(a) *Hypertonic saline.* Sodium chloride 140 grains dissolved in pyrogen-free distilled water, 1 pint (Metric equivalent 16 gm salt in 1 litre)

1 litre)

METHOD

Intravenous injection of 'hypertonic' or isotonic saline is given to all dehydrated or collapsed patients The first pint of saline should be administered immediately the patient is admitted Subsequent dosage may be calculated by clinical assessment of the degree of dehydration or shock, or by estimating the specific gravity of the blood, which is raised as the result of prevailing haemoconcentration

If the systolic pressure is 80 mm Hg or less, and if the specific gravity

the surface of a series of mixtures of glycerin and water of known specific gravity, ranging from 1054 to 1070 and starting from the highest The specific gravity is taken as being equal to that of the fluid in which the drop of blood remains suspended where it was discharged.

Some authors advise the measurement of the specific gravity of the plasma rather than that of the whole blood The method is similar, except that graded copper sulphate solutions are used instead of glycerin The figures corresponding to the above as S G plasma (i) 1025 to 1030; (ii) 1031 to 1040, (iii) 1041 or over

Shock often responds to saline therapy If not, it is counteracted by injection of a pint of plasma after the first injection of hypertonic saline

It may be necessary in the collapsed patient to cut down to the vein Otherwise the infusion is given through a wide bore needle into any convenient vein

over 50 per cent Even under epidemic conditions, however, the death rate of patients treated in hospital, who must be regarded as a highly selected population, is usually not greater than 10 per cent

In any outbreak there are many mild cases which recover spontaneously or respond remarkably quickly to treatment, and there are probably many more cases without symptoms.

DIAGNOSIS

In an outbreak the clinical diagnosis of the individual case is easy. Doubtful cases must be treated as cholera Any condition leading to acute dehydration with watery diarrhoea and vomiting may be mistaken for cholera Choleraic and algid pernicious malaria, acute food or chemical poisoning and heat exhaustion are all examples of related clinical pictures

The diagnosis of an isolated case may be difficult. The presence of vibrios may be confirmed in wet or stained stool preparations. Further identification of the organism is essential The vibrio can often be isolated by inoculation of specimens of faeces into alkaline peptone water and incubation at 37° C for 6 to 8 hours The ordinary faecal organisms are partly inhibited by the alkalinity and the vibrio becomes concentrated at the surface of the medium Further bacteriological identification is then simplified

TREATMENT

Treatment of established cholera is essentially a matter of non-specific measures for restoring the biochemical balance of the body and plasma volume. Specific measures designed to destroy the vibrios or neutralize hypothetical poisonous products are of secondary importance in the established case.

REPLACEMENT OF WATER AND SALT

The fluid and salts lost by evacuation must be replaced parenterally as rapidly as possible.

experience claim that the hypertonic solution is the more effective and

has no ill effects It thus appears to be perfectly safe to use either solution

Not more than two pints of hypertonic saline should be given in succession Thereafter further infusions should be administered as isotonic saline or mixtures of isotonic saline and 5 per cent glucose

The following details are modified from those followed in the Campbell Hospital in Calcutta

Solutions

(a) *Hypertonic saline* Sodium chloride 140 grains dissolved in pyrogen-free distilled water, 1 pint (Metric equivalent 16 gm salt in 1 litre)

(b) *Alkaline saline* Sodium chloride, 80 grains, sodium bicarbonate, 180 grains, dissolved in pyrogen-free distilled water, 1 pint (Metric equivalent sodium chloride, 9 0 gm; bicarbonate, 20 5 gm; water, 1 litre)

METHOD

Intravenous injection of 'hypertonic' or isotonic saline is given to all dehydrated or collapsed patients The first pint of saline should be administered immediately the patient is admitted Subsequent dosage

of the blood is (i) 1058 to 1060, 1½ pints of saline are needed immediately; (ii) specific gravity 1060 to 1062, 2½ pints, (iii) over 1062, 3 pints

The specific gravity is calculated as follows Blood is taken from the finger into a Pasteur pipette A drop is extruded from the pipette below the surface of a series of mixtures of glycerin and water of known specific gravity, ranging from 1054 to 1070 and starting from the highest The specific gravity is taken as being equal to that of the fluid in which the drop of blood remains suspended where it was discharged

Some authors advise the measurement of the specific gravity of the plasma rather than that of the whole blood The method is similar, except that graded copper sulphate solutions are used instead of glycerin The figures corresponding to the above as S G plasma (i) 1025 to 1030, (ii) 1031 to 1040, (iii) 1041 or over

Shock often responds to saline therapy If not, it is counteracted by injection of a pint of plasma after the first injection of hypertonic saline

It may be necessary in the collapsed patient to cut down to the vein Otherwise the infusion is given through a wide bore needle into any convenient vein

RATE OF ADMINISTRATION

The first pint of saline is given very quickly, i e. in about 5 to 10 minutes The second pint is given more slowly, in about 20 minutes. In a big man it may be necessary to give a further pint in 30 minutes, but usually after the second pint the rate of administration is slowed to about a pint in 4 hours

The injection of saline must be carried out with caution after the first phase of dehydration has been adjusted

Check should be kept on the urinary chloride concentration during treatment Once the chloride concentration begins to rise the saline-glucose mixture should be substituted for isotonic saline The mixture is made up by mixing isotonic saline and isotonic glucose in the proportion of 1 1 or 1 2

Infusion of saline must not be excessive. It is seldom necessary to give a total of more than 6 to 9 pints in the first 24 hours. An input/output account of fluid should be kept in all patients, and after dehydration has been adjusted the balance should be kept. It is fatal to overload the patient with fluid, especially if he is anuric.

Infusion of fluid usually brings about rapid recovery within a few hours It is rarely necessary to continue it for more than 24 hours except in cases in which evacuation or shock persist or reappear

Acidosis associated with the reduction in fixed base, and indicated by air hunger, and increasing restlessness, may be counteracted by injection of the alkaline saline or of bicarbonate solution (120 grains to the pint), but the injection of saline is often in itself sufficient to adjust the electrolyte balance.

One of the difficulties encountered in parenteral treatment is the

As soon as the patient is hydrated he should be encouraged to take fluid orally.

CHEMOTHERAPY

Destruction of the vibrio can be effected to some extent by the use of specific bacteriophage or sulphonamides Other methods have been recommended from time to time with indifferent success There is considerable doubt about the efficacy of phage At present the best approach to specific treatment seems to be the use of the relatively insoluble sulphonamides, such as sulphaguanidine, given in large doses corresponding to those administered in bacillary dysentery Drug therapy must not be relied on alone. It must always be accompanied by the non specific measures described above

The difficulty may be to administer the drug against the tide of vomiting.

Certain antibiotics including chloramphenicol and streptomycin are also active against the vibrio

No chemotherapeutic agent, however, has any striking effect on the clinical course of cholera, but sulphonamides and antibiotics rapidly reduce the vibrio content of the stool and may thus be of value in the early stages before dehydration is established and in shortening the time over which the stools remain infective, thus influencing the spread of the infection in the community Vaccines have no therapeutic effect

SYMPTOMATIC TREATMENT

Infusion of saline will usually bring about immense relief in all symptoms including muscle cramps, which may be very violent Severe pain may be relieved by self-administered chloroform on a handkerchief Most authors advise against the use of morphia. Atropine is sometimes recommended in the early stages The patient should be persuaded to take fluid by mouth if possible Such fluid should contain glucose Careful nursing is essential In the convalescent stage the patient must be kept quiet to avoid the recurrence of vascular collapse

L-noradrenaline infusion has been used successfully in combating shock

DIET

In the active stage the patient is unable to take more than sips of water or glucose solution by mouth As he improves he may be given glucose drinks, sugared barley, arrowroot, or rice water and buttermilk He is gradually brought back to a diet of soft rice, potato, fish, etc

IX

EPIDEMIC DROPSY

DEFINITION

A CONDITION caused by ingestion of the seeds of the Mexican poppy (*Argemone mexicana*) or their products, particularly in contaminated mustard oil, characterized in severe cases by oedema, vascular dilation and cardiac insufficiency.

GEOGRAPHICAL DISTRIBUTION

Epidemic dropsy is seen most commonly in India, particularly in Bengal, where most cases occur in Calcutta, and also in Bihar, Orissa and Central and United Provinces It has appeared in Mauritius, Fiji and South Africa.

AETIOLOGY

The toxic agent is contained in the seeds of *A mexicana* which grows as a weed amongst the mustard crops of India The seeds are very similar to those of the mustard plant and may be mixed with the latter by accident or deliberately as an adulterant in the manufacture of mustard oil In the recent outbreak in South Africa the seeds were found as a contaminant of cheap badly sieved wheat.

In India epidemic dropsy appears amongst rice eaters who use mustard oil for cooking. It is commoner in the middle class than in poor people who cannot always afford mustard oil and have to use substitutes. The incidence varies considerably from year to year. In India it is highest during the rains or soon after, the maximum occurring in July or August, the minimum in April The maximum incidence [illegible]

children under the age of 4 rarely All other age groups are involved The sexes are affected equally.

The apparent racial distribution of the condition arises from dietetic habits. Wherever Bengali food is eaten and mustard oil can be contaminated, epidemic dropsy may appear.

The syndrome rarely occurs sporadically It usually appears in groups of individuals on the same diet Only a few families in scattered districts may be affected, but at irregular intervals there may be serious outbreaks involving large numbers of people. All those affected in India will be found to be on the typical rice-mustard oil diet.

Various extracts of argemone seeds have been found to have physiological effects resembling some of the features of the syndrome. The true toxic factor is an alkaloid The seeds have been fed experimentally to animals and man with variable results; in some instances syndromes very similar to those of epidemic dropsy have been produced in man.

It has been suggested that the toxicity of the seeds is conditioned by the diet, and rice was believed to be one of the deciding factors, since it was reported that the addition of rice to the diet exacerbated the symptoms In view of the outbreak amongst wheat eaters in South Africa it is difficult to incriminate rice specifically It is more likely that malnutrition and deficiencies are the conditioning factors, especially in those, like rice eaters, who live on a high carbohydrate low protein diet

PATHOLOGY

The basic physiological change is a generalized severe vasodilatation affecting capillaries and small vessels, particularly in the skin, heart muscle and the uveal tract. The early oedema has been explained by increase in capillary permeability and an accompanying retention of tissue salt The late oedema results from heart failure

Irregular formation of new blood vessels is common in many tissues, particularly beneath the skin In some cases and in some epidemics but [illegible]

[illegible] secondary anaemia may develop, often complicated by the effects of concurrent deficiencies

Vascular dilatation involving the iris and ciliary body not uncommonly leads to raised intraocular pressure and glaucoma Optic atrophy develops in untreated severe cases

At autopsy vascular congestion and dilatation of the skin, the liver and other organs is notable In the heart muscle there may be oedema, intense congestion and considerable new capillary formation. In cases complicated by myocardial insufficiency the characteristic enlarged 'congested' liver develops

Anaemia This is of moderate intensity in severe cases The cells are [illegible] emia, [illegible] esent

The electrolyte concentration is low.

CLINICAL PICTURE

The clinical picture varies widely It is probable, especially in 'epidemics', that in many cases the signs are so mild as to be overlooked.

In patients in the same feeding group, for instance members of the same family, the syndrome also appears in varying intensity. Some outbreaks are notable for the severity of the cases; others for their mildness. It is believed that these variations depend to a considerable extent on the dose of toxic agent absorbed

In most cases the onset is insidious In more severe cases it may be sudden. In experimental cases there is a latent period of some days after taking contaminated oil before the appearance of symptoms. In the field the patient may give a history of a few days of anorexia, nausea and looseness or diarrhoea before the onset of oedema Severe cases begin acutely and may end fatally in a matter of days.

Oedema occurs in all cases Other signs vary in incidence and intensity from case to case and from outbreak to outbreak.

The usual moderately severe case complains of weakness, breathlessness on exertion and swelling of the feet and legs. There is often mild fever, the temperature rarely exceeding 102° F. Nausea is common and there may be some vomiting. In some patients diarrhoea is a prominent and difficult feature; in others it is absent

The oedema is soft and easily pitted It is usually confined to the lower extremities and appears rapidly. In ambulatory patients it becomes worse at the end of the day. Very rarely there may be general anasarca In severe cases there may be effusions into the pleural cavities and pericardium. Lung oedema may appear in the terminal stages.

The patient's chief concern is usually dyspnoea often present even at rest and worsened by exertion. The pulse is fast and thready; the diastolic pressure may be very low In severe cases the heart is dilated, the apex beat is displaced to the left, the basal dullness to the right. Systolic apical murmurs are common The electrocardiogram shows signs of myocardial involvement. There may be frequent extrasystoles or sinus tachycardia In fatal cases the signs of acute heart failure develop The pulse may become irregular and fibrillating, and the liver enlarges and becomes tender. Heart failure may develop progressively over a few days, or appear suddenly and lead to a fatal issue

Peripheral vascular changes appear in most cases. Irregular bluish mottling of the skin with dilated vessels is common. In moderately severe cases these changes develop a few days after the appearance of the oedema They may be evident from the beginning in acute cases

Subcutaneous telangiectases and haemangiomata appear in some cases; they may be common in some groups of patients, absent in others

The haemangiomata (also called 'sarcoids') usually become defined after the original skin vascular dilatation has subsided, and progress steadily to become small tumours raised above the surrounding skin and sometimes sessile, ranging in size up to about half an inch across

They may bleed freely after injury They gradually reduce in size during convalescence and finally disappear

In some patients in the acute phase there may be tenderness of the calf muscles, increased or absent knee jerks and widespread tingling, burning feelings in the skin Pareses are uncommon, except in the presence of vitamin deficiencies

One of the most serious complications is the development of glaucoma, which may result in blindness As many as 5 to 10 per cent of patients in some outbreaks may show evidence of pathologically raised intraocular pressure, including dimness of vision, contraction of visual fields and subjective rainbow haloes There is often surprisingly little ocular pain

Abortion or stillbirth is common

COURSE AND PROGNOSIS

• The signs and symptoms in the case of average severity subside on rest in bed The patient may be little affected so long as he remains at rest, but may suffer exacerbation of the cardiac condition on exertion Convalescence is slow and it may be weeks or months before he can return to work

Some cases are very severe from the beginning and fail to respond to treatment, dying in cardiac failure in a few days

The death rate varies from outbreak to outbreak It is usually about 5 per cent, in some outbreaks rates as high as 50 per cent have been recorded

In the individual case the prognosis largely depends on the cardiac state It is bad when decompensation has appeared In some cases severe and even fatal cardiac symptoms may develop during treatment Prognosis must therefore be guarded in all cases

DIAGNOSIS

The diagnosis is easy in a recognized outbreak The dietetic history of the patient should give the necessary clue

The appearance of acute oedema in several members of a family or similar groups known to be using mustard oil is highly suggestive Cases which begin with diarrhoea may be missed, and there may be some confusion with wet beri-beri or famine oedema, both of which usually develop more slowly In beri-beri nervous lesions may be prominent and the response to thiamin therapy is usually dramatic Careful investigation of the diet should help to settle the diagnosis in both beri-beri and famine oedema It is possible, however, for both to occur concurrently with epidemic dropsy, in which there is usually some background of general dietary inadequacy

TREATMENT

The patient must be put to rest in bed and given a diet from which the suspected oil or seeds are absent

A high protein diet with moderate content of fat and carbohydrate is essential In India it is customary to substitute other grain for rice

An initial saline purge is indicated in diarrhoeic cases. Sodium sulphate one half ounce is given immediately, one quarter ounce is given subsequently as required

Heart failure may or may not respond to digitalis In any case this drug should be tried If unsuccessful a combination of mersalyl and ammonium chloride may often be beneficial

Obvious dietary deficiencies should be corrected Vitamins B and C are often required to adjust the diet, but no immediate response to the former is to be expected It is probably simpler and equally effective to add yeast or vegetable extracts, cod liver oil and citrus fruit

In view of the evidence of salt retention the salt intake should be limited during the acute stages.

Haemangiomata do not require treatment unless they bleed, when pressure is usually effective

Glaucoma may need surgical interference. Eserine is not effective A careful watch for increased ocular tension should be kept in all patients, as the eye changes may appear in apparently mild as well as obviously severe cases

Convalescence is likely to be slow, particularly in cardiac cases.

PREVENTION

Public health measures should prevent the use of contaminated oil or wheat, and should aim at the extermination of *A mexicana* and the avoidance of contamination before the mustard oil is processed

Tests for the presence of argemone oil in mustard oil Simple chemical tests for the presence of the toxic factor in mustard oils have been devised The standard procedure is as follows

A sample of suspected mustard oil is shaken for 2 minutes in a test tube with an equal quantity of clear nitric acid If more than 1 per cent of argemone oil is present a yellowish brown precipitate forms and collects in the bottom of the tube A positive reaction indicates the presence of a toxic dose

X

EPIDEMIC HAEMORRHAGIC FEVER

DEFINITION

AN acute disease which possibly is infective, but so far is of unproven origin and causation It is characterized by marked fever and constitutional symptoms, by increased capillary permeability with haemorrhages, and by renal damage

GEOGRAPHICAL DISTRIBUTION

Various forms of haemorrhagic fever for some time have been known to occur endemically, and sometimes epidemically, in parts of Russia and South Eastern Siberia, in Manchuria and in Korea The concentration of European and other troops in Korea in 1951 and 1952 was attended by the appearance of a form of this condition among them, and thus its introduction to Western medicine Comparable conditions, such as the epidemic nephropathia reported in Scandinavia and Finland, may be of similar aetiology and therefore extend the known geographical distribution of the disease

AETIOLOGY

This so far is not known The seasonal incidence and localized distribution of the disease have suggested that an arthropod, probably a trombiculid mite, is a factor in its acquirement The course of the disease has suggested a virus causation, but no virus has been identified Cross-infection in man has not been recorded and attempted animal infection has been unsuccessful

PATHOLOGY

The majority of deaths occur during the first two weeks, the usual immediate cause is peripheral circulatory failure, which commonly is associated with uraemia Pulmonary oedema or haemorrhage into a vital organ may cause death Histological studies show the presence in all organs of a combination in varying degrees of capillary dilatation and engorgement, haemorrhages, focal coagulative necroses due to infarcts, and a sparse cellular infiltrate The kidneys particularly are involved, it is the medulla, not the cortex, which is affected There are varying degrees of degeneration of the tubules, which may be widely separated by haemorrhages, infarcts surrounded by haemorrhage are

scattered throughout the medulla. The pituitary gland, heart and suprarenals contain haemorrhages and infarcts; other organs and tissues suffer less constantly.

Abnormal capillary [illegible]

and peritoneal sacs are usual, and tissue oedema is evident. The greatest amount of fluid is found in the retroperitoneal tissues in the form of a gelatinous mass Patients dying late in the disease tend to be dehydrated

CLINICAL PICTURE

The incubation period is about a month The course of the disease broadly can be divided into three stages: the invasive or febrile phase, [illegible]

abruptly and persists irregularly for up to 6 days. There is great thirst, and often nausea and vomiting which are aggravated by taking excessive fluid Petechiae appear in the skin and mucous membranes after the third day; they are readily induced by minor injury. There is slight general lymphatic glandular enlargement, but the spleen and liver are not enlarged Vomiting may be constant and troublesome There are aches and pains especially in the belly and the back Marked albuminuria suddenly develops towards the end of the fever, between the fourth and sixth days of illness The specific gravity of the urine initially is high; but red cells and casts soon appear and the specific gravity of the urine falls and its volume lessens

The toxic phase follows the ending of the fever by rapid lysis but the patient's condition worsens; backache becomes severe Usually there is some hypotension, in a minority this is marked (60/50 mm) and is accompanied by other signs of shock over a period of a couple of days Haemorrhages increase, and occur from the nose, lungs, stomach and kidneys, slight injuries result in large ecchymoses At the end of the first week the haematocrit reading, red cell count, and haemoglobin value rise markedly with a reduction in circulating plasma volume Facial and periorbital oedema already evident increases, and there is oedema of the conjunctivae. As this stage ends, the signs of shock diminish and the haemorrhages and oedema subside; fluid accumu- [illegible]

falls Oliguria may last only a day or so, or for several days and progress

to anuria The blood pressure rises to a hypertensive level with an apparent or relative increase in circulating blood volume which is really due to diminished vascular capacity, there is venous distension and even pulmonary oedema in some cases The blood urea level rises and [illegible]

passed, this may upset the electrolyte balance The blood urea level falls slowly and albumen, cells and casts disappear from the urine as the patient enters convalescence It may be three to six months before a normally concentrated urine is passed, full physical and psychological recovery is slow

Throughout the illness after the third day there is a leucocytosis (12,000 to 24,000 cells per cmm) of a leukaemoid type The platelet count commonly is lowered, but not sufficiently so to account for the haemorrhagic tendency

TREATMENT

None is specific and drugs as a whole are better avoided The essentials for the welfare of the patient are minimum movement, restriction of fluids, and competent nursing Absolute rest must be [illegible]

sometimes is distressing and exhausting, has been relieved by 4-5 ml ether or 8 per cent magnesium sulphate solution given intramuscularly Convalescence after recovery must be slow and protracted The possibility of later renal troubles must be envisaged in view of the damage the kidney has sustained

XI

FILARIASES

FILARIASIS (BANCROFTIAN AND MALAYAN)

DEFINITION

INFECTION with parasitic nematodes *Wuchereria bancrofti* and *Brugia malayi*, the adults of which inhabit the lymphatic tissues. The clinical effects range from none to elephantiasis

GEOGRAPHICAL DISTRIBUTION

Bancroftian filariasis is widely spread in the tropics and subtropics It occurs in the West Indies, South America as far south as the Argentine; southern Spain, the African Mediterranean seaboard, West, Central and East Africa; Madagascar; the Middle East, India, Burma, southern China, Malaya; southern Korea, Japan; Indonesia, Northern Australia, many Pacific Islands, including Samoa and Fiji It existed until recently in the southern United States.

Malayan filariasis is much more restricted In some areas it occurs alone, in others it overlaps with bancroftian It is found in large areas of Malaya, Indonesia, Borneo and New Guinea, and in pockets in India, Indo-China, Ceylon and southern China

AETIOLOGY

THE CAUSAL ORGANISMS IN THE HUMAN HOST

The development of the worms in the human host is practically identical. The adults are very fine filiform creamy-white short worms. They may be found coiled together in the larger lymphatics near the aorta, in the pelvis and genitalia and in the lymphatic glands Mating occurs in these areas The females are viviparous, and embryos are passed in large numbers into the lymphatics The embryos or microfilariae are sheathed. They ultimately escape from the lymphatics and appear in the peripheral blood

It probably takes 3 to 6 months or longer for the larval forms injected by the vector to reach full maturity It is not known how long the individual adult may survive in the host but it is obviously a matter of years

The anatomical features of the microfilariae of *W. bancrofti* and *B. malayi* differ in some respects. The differentiation of the one from the other is referred to later

PERIODICITY

In most endemic areas the microfilariae of both *W. bancrofti* and *B malayi* appear in greatest numbers in the peripheral blood during the night somewhere between 10 p m and 2 a m and may be very scarce during the day, when they probably concentrate in the pulmonary vessels This nocturnal periodicity has never been satisfactorily explained It is not always present Nocturnal periodicity may sometimes be reversed by inverting the sleeping and waking habits of the infected individual It is commoner in regions where the vector is a night feeder Non-periodic varieties are found in many endemic regions, especially in the Pacific Islands Some authorities consider these are representatives of a separate species, *W pacifica*

TRANSMISSION

Bancroftian filariasis is transmitted by the bite of several genera and species of mosquitoes The most widely distributed vectors are species of Culex, Aedes and Anopheles

Malayan filariasis Mosquitoes of the genus *Mansonia* are the principal vectors, although some infection may be transmitted by *Culex* and *Anopheles* Because of the breeding habits of the main vector malayan infections are found near water containing the water lettuce *Pistia* Cats, dogs and other animals may harbour *B malayi* The problems of control of this infection are thus very different from those of bancroftian filariasis

THE CAUSAL ORGANISM IN THE VECTOR

The insect becomes infected by ingesting human blood containing infective microfilariae After ingestion the microfilaria escapes from the sheath, penetrates the gut wall of the insect and passes to the thoracic muscles where it undergoes a series of moults After two or more weeks the infective larvae reach the proboscis, it is not certain how they reach the human tissues after the insect bites

EPIDEMIOLOGY

Transmission in a given area depends on the presence of suitable vectors in large enough numbers, and on an adequate human reservoir of infective microfilariae The suitability of the human reservoir depends to some extent on the stage of clinical development Infective microfilariae are found in the blood in large numbers in most cases during the inflammatory and early obstructive stages In advanced cases of elephantiasis circulating microfilariae are rarely present and the patients are non-infective

In many regions the main sources of infection are asymptomatic cases in which large numbers of microfilariae may be present in the blood

The infection of the vector depends to some extent on its habits. Night feeders are likely to be more effective in transmitting filariasis in which there is pronounced nocturnal periodicity. Day feeders are more likely to be concerned with the transmission of non-periodic strains

Continued reinfection over a long period is apparently necessary for the development of the full clinical condition, which occurs much more frequently in natives of endemic areas than in visitors.

There is, however, no racial immunity Some acquired resistance is thought to be developed and may be responsible for some of the manifestations of the disease

The sexes acquire the disease equally when the risks of infection are equal The preponderance of infection in one sex often results from increased opportunity of infection, usually arising from occupation.

Clinical filariasis is uncommon in very young children, probably because of the time required by the worms to reach maturity in the host Microfilariae are seldom found in the blood in children before the age of 3 or 4 years Very rarely clinical signs have been observed in children at the end of the first year of life The disease commonly develops first in youth or early adult life

PATHOLOGY

Pathological changes in the tissues are induced chiefly by the adult worms, living and dead, directly by their presence, or indirectly by the production of some soluble toxic factor The microfilariae circulating in the blood stream are probably not involved Certain local reactions may be allergic in nature

Secondary infection may be important in the production of lesions especially after the death and necrosis of the worm, and in the later stages of elephantiasis

The minor manifestations of the infection, such as the fleeting tissue oedemas and erythemas, probably arise as sensitivity reactions resulting from partial immunity responses to the presence of both adults and microfilariae

INFLAMMATORY AND EARLY OBSTRUCTIVE STAGES

Changes occur principally in the lymphatic vessels and glands and in the connective tissue The most marked reactions occur about adult worms lying in lymphatics, especially when the worm has died and started to degenerate Local reactions may appear, however, in the absence of worms

The characteristic lesion is a granulomatous lymphangitis, usually slowly progressive but subject to acute exacerbations. It develops in the

tissue immediately associated with a lymphatic vessel or a series of vessels in which there may be adult worms The tissue becomes infil-

of epithelioid nests and giant cells The local blood vessels are dilated and usually show some cuffing with round cells Nodules of cellular granulation tissue are formed in this way which press in upon the lumen of the lymphatic vessel and tend to occlude it The endothelium of the vessels may become hypertrophic, also leading to endovascular occlusion or lymph thrombosis Sometimes the process goes on to necrosis and pus formation Abscesses may discharge to the surface and lead to the development of persistent sinuses Finally, the granulomatous tissue and occluded vessels are replaced by fibrous tissue

Where the lesions develop around superficial lymphatics there is commonly some hard oedema and erythema of the overlying skin

The affected vessels show clinical signs of obstruction, becoming dilated, distorted and tense with lymph The irregular development of granulomatous tissue gives the whole mass a lobulated feel and appearance

In some regions the dilated vessels may rupture into the surrounding tissues and nearby hollow viscera

The lesions which develop in the lymph glands are essentially the same as those about the lymphatics The sinuses may contain adult worms and in the vicinity of these granulomatous tissue develops, with epithelioid cells and giant cells, surrounded by lymphocytes and plasma cells Eosinophils may be present in large numbers at the outskirts of the inflamed area, they are said to be most numerous when the worm is dead As in the lymphatics, the lesion may proceed to fibrosis or to abscess and sinus formation Obstruction to local lymph flow is caused and may lead eventually to elephantiasis

The obstruction of the flow of lymph from the drainage area brought about by these changes in lymph vessels and glands leads to the development of oedema which is at first soft but eventually becomes firm The tissues involved may gradually undergo elephantoid changes

ELEPHANTIASIS

There is a gradual increase in thickness of all the tissues The epithelium thickens irregularly in all layers, in some areas the hypertrophy exceeds that in others and warty excrescences develop The connective and fatty tissues thicken and change into an oedematous myxomatous mass irregularly infiltrated with lymphocytes and eosinophils The subcutaneous lymphatics and spaces increase in number They become distended and lobulated and may rupture on to

the surface, as in lymph scrotum. In the limbs the muscles at first hypertrophy but later atrophy

The thickened tissue comes to hang in folds. Elephantoid areas of the skin of the trunk often hang forward on pedicles of normal skin In the folds of the elephantoid skin secondary infection may invade the deeper tissues and lead to acute inflammation and necrosis and eventually fibrosis It is difficult to assess the importance of secondary infection in building up the final condition

In the early stages of elephantiasis there may be acute lymphatic inflammatory episodes similar to those described above Biopsy may reveal the presence of worms in the lymphatics or glands. X-ray may disclose the presence of calcified worms

The local lymph glands are nearly always affected

CLINICAL PICTURE

INCUBATED PERIOD

In natives of endemic regions who are open to repeated reinfection it is not possible to estimate the incubation period Study of individual European cases and cases in troops stationed for short periods in endemic areas in the Pacific during World War II has indicated that the incubation period is probably of the order of 8 to 12 months because of the slow maturation of the worms Repeated infection appears to be necessary for the development of the full clinical picture.

The clinical features of the early stages of filariasis may be separated to some extent into those which are inflammatory and those which are obstructive It should be realized, however, that such division is artificial and that all stages may overlap considerably Many cases of advanced filariasis may give no history of early involvement of the lymphatic system, and on the other hand obvious infection with blood invasion by microfilariae may exist without any contemporaneous or subsequent development of clinical signs or symptoms.

THE ONSET

The condition first appears most commonly in young adults after frequent exposure to reinfection. The onset is sometimes slow and insidious Search into the patient's history will, however, often reveal one or more febrile or inflammatory episodes

FILARIOID OR ELEPHANTOID FEVER

[illegible]

disappear in a few days to a week. There may be no rigor and only mild fever There is usually vigorous sweating For some days before

the onset and during the fever the patient suffers from malaise and anorexia Nausea and vomiting are common during the attack, frequently accompanied by a feeling of deep depression which often persists after the fever has subsided

After a variable but short period the fever subsides and the patient may completely recover, only to develop further brief febrile attacks, followed by remissions until the acute inflammatory local reactions appear

INFLAMMATORY REACTIONS

These local reactions are expressions of inflammatory changes in the lymphatic vessels and glands and are very varied in their distribution and intensity They consist essentially of lymphangitis, lymphadenitis and abscess formation They tend to recur in areas in which they first appeared, and to develop into obstructive lesions They are usually accompanied by varying degrees of fever The advanced case usually gives a history of a series of local reactions in the parts of the body affected by elephantiasis, but this is not always so

Lymphangitis

Acute involvement of lymphatic vessels is common, especially in the extremities, the legs in bancroftian infections and the arms in malayan infections The inflammation is usually accompanied by high fever, sometimes with rigors, and severe toxaemia

The affected vessels are acutely tender, easily palpable and the overlying skin is usually turgid and erythematous, so that the inflamed vessels are etched on the skin as bright red streaks

The condition is sometimes accompanied by very itchy irregular fleeting hard erythematous swellings of the skin scattered over the body, which may sometimes appear in the absence of local lymphangitis

The lymphangitis tends to be centrifugal in its distribution For instance, it commonly starts in the lymphatics near the femoral glands and proceeds downwards in the leg

In the legs the femoral and malleolar vessels are most frequently affected The inflammation may be unilateral or bilateral In the latter case, one side is frequently involved much more severely than the other

The vessels of the spermatic cord and testis are especially susceptible Funiculitis and orchitis are the commonest and most severe manifestations of the early stages of the disease

Lymphatic vessels anywhere in the body may become involved and cause local effects which may simulate other conditions For instance, inflammation of abdominal lymphatics may suggest acute abdominal states, with deep tenderness and muscular rigidity

Sometimes small abscesses may form in the affected vessels or glands

site of an abscess is often indicated at an early stage by extreme tenderness over the area involved, the so-called 'focal spot'.

Lymphadenitis

In association with the lymphangitis there is almost always some local adenitis. This frequently precedes the appearance of the lymphangitis. The glands are swollen, firm and tender. They remain discrete unless there is abscess formation. There is usually some hard oedema of the overlying skin.

The glands most commonly affected are those in the groin and the epitrochlear regions. The latter are commonly enlarged in malayan and pacific infections before any other manifestations of the disease. Such glandular enlargement tends to persist. The glands sometimes contain adult worms.

Funiculitis and 'Orchitis'

and tenderness disappear in quiescent periods but some induration remains. Thickening of the cord is one of the earliest signs of filariasis and must always be carefully looked for.

'Orchitis' begins suddenly with very severe local pain greatly exaggerated by movement and pressure. The patient is completely incapacitated. The organ is enlarged and exquisitely tender. The epididymis is usually swollen and acutely tender; occasionally there may be epididymitis only. The scrotal skin may be oedematous and erythematous and there is almost always an associated severe funiculitis. Orchitis is often unilateral but may be bilateral. It is sometimes associated with acute hydrocoele.

The acute symptoms and signs last a few days and then almost completely subside. After a variable period they recur and the condition progresses through episodes of attack and remission to recovery or to

In the intervals of quiescence the epididymis may remain enlarged, and the cord is usually thickened and nodular along its whole length.

Hydrocoele commonly develops in recurrent cases of orchitis

The stage of intermittent acute inflammation may stretch over months or years and cover successive advances of the disease towards the fully developed obstructive stage Within a few months of the onset, however, the two stages usually begin to overlap

OBSTRUCTIVE SIGNS

The obstructive signs develop usually in parts of the body where inflammatory reactions have occurred They may sometimes appear without previous local inflammation Obstructive phenomena arise from interference with local lymphatic drainage or circulation and consequent accumulation of fluid within the vessels and in the interstitial tissues The affected vessels may eventually rupture

Obstructive signs include oedema, varices of local lymphatic vessels, lymph scrotum, hydrocoele and other local accumulations of fluid

The signs of obstruction to lymph drainage are usually progressive and often associated with irregular bursts of local inflammation involving both vessels and glands

Varices Distension and varicosity of lymphatic vessels is especially common in the superficial vessels of the femoral, inguinal and testicular regions More deeply placed lymphatics such as those of the abdomen are also involved The appearance of a varix may be the first indication of the disease, but a careful study of the clinical history will usually disclose previous local inflammatory episodes.

The vessels involved are distorted, tense and distended with fluid, superficial vessels may be partly emptied by massage away from the local glands, which are almost always enlarged Deeper varices such as those in the scrotal vessels may often be felt as collections of tense cords, or may not be discovered until operation, for example at the removal of hydrocoele

Varices tend to be slowly progressive and are usually painless There may be occasional periods of acute exacerbation In periods of quiescence the skin is freely movable over the affected vessels, in exacerbations it may become oedematous and erythematous Occasionally the whole limb may become oedematous

Abscesses may form around varicose vessels and burst on to the surface leading to chronic sinus formation

Varicose vessels may become inextricably mingled with local enlarged lymphatic glands, forming an irregular mass of tissue which is sometimes known as varicose glands The glands remain discrete except after necrosis following secondary infection, when they may become matted together

Lymph scrotum The lymph drainage of the scrotal area is often obstructed early in both forms of filariasis, usually in association with

enlarged inguinal glands The skin and subcutaneous tissues become swollen and oedematous, the lymphatic vessels become dilated and tense with fluid The skin becomes erythematous and covered with small vesicles varying from a millimetre to a centimetre in diameter containing clear or milky fluid in which microfilariae are commonly present The vesicles rupture so that the skin surface becomes constantly wet with escaping fluid Secondary infection occurs almost inevitably and small abscesses are formed which discharge pus and eventually form sinuses The whole scrotal skin may be affected and becomes greatly coarsened and thickened, eventually passing on to elephantiasis.



FIG 6 Filariasis bancrofti
Elephantiasis of leg and scrotum
(Note left femoral varix and gland mass)
[Courtesy Dr T H White]

The onset of lymph scrotum is often accompanied by some fever, and general reaction Hydrocoele is present in the majority of cases. There is usually a history of former acute involvement of the cord and testis

Hydrocoele· Gradual effusion of fluid into the cavity of the tunica vaginalis is a common result of earlier inflammation and obstruction of the lymphatics draining the testicular region The fluid may be clear or milky; it usually contains microfilariae. There may or may not be a history of one or more acute attacks of orchitis or epididymitis or both and acute episodes may be repeated after the hydrocoele has formed, leading to increase in the size of the tumour

The condition is most commonly bilateral. The regional glands are usually enlarged and there are often concomitant varices of the superficial lymphatics of the scrotal sac and sometimes oedema of the scrotum and lymph scrotum

Effects of obstruction and varicosity of deep lymphatics Ascites, pleural effusion and synovitis may all appear as a result of interference with local lymph drainage.

Obstructed varicose lymph vessels in the abdomen may eventually rupture.

The most striking clinical picture resulting from rupture is *chyluria*. In this condition vessels containing chyle burst through into the urinary tract, their contents escaping into the kidney pelvis, the ureters or the bladder. The patient passes a milky mixture of chyle and urine.

Albumin is always present On standing the fluid settles into three layers; an upper thin layer of fat, a deep middle layer of semicoagulated lymph and urine, and a lower usually pink layer of debris and cells, including erythrocytes Microfilariae are often present

Chyluria usually develops abruptly It may be preceded by loin pains and accompanied by fever and some prostration but there may be no accompanying general symptoms Milky urine is passed for two or three days at a time Attacks tend to be recurrent with long quiescent intervals of weeks or years. In rare instances coagulation of the chyle may cause obstruction to urinary flow and retention of urine The passage of coagula may cause renal colic

Lymphatics containing lymph and not chyle may also occasionally rupture into the urinary tract, leading to the passage of blood-stained urine containing lymph This condition has been called *lymphuria*

Lymph or chyle may occasionally escape direct into the abdominal cavity giving rise to lymphatic or chylous ascites In such cases the symptoms at the time of rupture may resemble acute peritonitis Escape of chyle may also lead to chylocoele, clinically indistinguishable from hydrocoele except that the fluid content is milky

ELEPHANTIASIS

In regions of high endemicity the majority of cases of elephantiasis probably arise from filarial infection The condition is, however, basically the end result of chronic lymphatic obstruction and may arise from causes other than filariasis It is not always possible to say for certain whether in a given case filarial infection is the cause, but there is often a history of repeated attacks of local lymphangitis and adenitis *interspersed with remissions of variable length and the gradual advance of the tissue lesion to fully developed elephantiasis In some cases there* is no such history, the development being continuous without any particular localizing incidents In the great majority of cases, however, there is a clear history of long exposure to infection The apparent necessity for frequent reinfection in the production of elephantiasis probably explains the age incidence of the condition, which develops late in the disease in young adults and is rare in children

In some cases elephantiasis may appear or develop during a period in which the more active inflammatory or obstructive phases of the disease are going on in the same anatomical region or elsewhere in the body In most cases, however, the full development is met after the signs of active filariasis have ceased

The prevalence of elephantiasis varies widely in endemic regions In some regions such as Samoa, the condition is exceedingly common, in others, such as certain areas of China, it is rare

The distribution of the lesion in the body is also very variable and



Fig 7 Filariasis bancrofti
Elephantiasis of scrotum
[Courtesy Dr C C Chesterman]



Fig 8 Scrotal hernia.
Important in the differential diagnosis of elephantiasis

depends to some extent on the geographical locality and the type of infecting filaria In bancroftian infections one or both of the lower extremities with or without the scrotum are most commonly involved Elephantiasis in the leg is most frequently seen below the knee but the whole limb is often involved The upper extremities, the breasts, the labia may also be affected In malayan infections the legs and arms are about equally concerned in some regions, the arms most often in others, and scrotal involvement is uncommon Some authors claim that the site of election for the appearance of elephantiasis may be determined by constantly repeated trauma Thus, horse or bicycle riding may influence the development of scrotal elephantiasis

The part played by secondary infection in the development of elephantiasis is uncertain On the whole, it is probably of minor importance

The regional lymph glands are usually involved, the inguinal and femoral glands in elephantiasis of the legs and scrotum, the axillary and epitrochlear in elephantiasis of the arms The glands are large, firm and discrete except where abscess has occurred When the arm is involved one or more of the axillary glands are often enlarged enormously in the very early stages and serve as a useful diagnostic indication

Elephantiasis arises as a thickening of both the skin and the underlying tissues, its progress can perhaps best be followed by a specific example, say, in the leg

The femoral and inguinal glands are probably enlarged after a series of previous attacks of adenitis There may be varices and obstructive lesions in the lymphatics, for example, in the femoral region Oedema of the lower half of the limb may come on slowly and gradually spread from the ankle eventually up to the thigh At first the oedema is soft but as time goes on, in the course of months or years, the character of the oedema changes and it becomes hard The skin epithelium hypertrophies and in places wart-like thickenings appear The subcutaneous tissue changes in structure There is oedema, increase in number and dilatation of lymphatic vessels, sometimes local varices All soft tissues tend to increase The limb becomes noticeably thickened and eventually enormous, the changes developing most rapidly below the knee At first the muscle hypertrophies, but later atrophies and is partly replaced by myxomatous fibrous tissue At this stage the efficiency of the limb suffers and the patient often finds it difficult to get about As the limb increases in size the skin billows out in irregular folds in the creases of which secondary infection is common

All stages are met from slight uniform swelling with oedema and thickening of the skin to enormous grotesque enlargements

Changes in other parts of the body are essentially of the same kind

Scrotal tumours may reach immense proportions Some have been recorded weighing over 200 lb The penis is not usually affected in scrotal elephantiasis but is completed retracted within the tumour, the urine reaching the surface along a tube of skin pulled out by the hypertrophic mass The inguinal glands are generally enlarged and discrete and there may be local evidence of lymphatic obstruction, such as varices. The testes are dragged down by the tumour, and may be found attached to the under part of the scrotum; the cords are greatly lengthened In spite of this anatomical strain, however, the testicular function may be unaffected Most cases have bilateral hydrocoele.

Other parts of the body may be involved including the penis (usually without involvement of the glans), circumscribed areas of skin on the trunk (especially the lower abdominal wall), neck or limbs, and occasionally the tongue and the nose.

COURSE AND PROGNOSIS

The progress of the disease is slow It usually takes years for the full development to be reached.

Filariasis is much more likely to progress to elephantiasis in a native of an endemic area than in the infected visitor. In the early stages of the disease removal of the latter from the endemic region will be followed by gradual recession of the signs and symptoms and recovery.

Once elephantiasis has commenced the future development will depend on care and treatment, including the prevention of sepsis In the early stages the prognosis may be improved by suitable chemotherapeutic measures, which are considerably less effective later

It is impossible to estimate the prognosis of the asymptomatic case in whom microfilariae are present in the peripheral blood. Some of these cases in young people probably proceed to the advanced disease

The likely development of elephantiasis in a group of individuals may be assessed to some extent by the characteristics of the disease and the frequency of its appearance in the particular geographical region concerned In Samoa, for instance, the probability of ultimate elephantiasis is high, in other areas it is low

DIAGNOSIS

Clinical. Many infected persons will have no clinical signs and the diagnosis can be made only by discovery of microfilariae in the blood or tissue fluid (see later)

found in the epitrochlear and axillary regions or in the groin Diagnosis from other causes of asymmetrical gland involvement is difficult, but careful inquiry may elicit a helpful history of febrile attacks and possibly of acute local adenitis and lymphangitis; microfilariae may be found in the blood

The differential diagnosis of filarial lymphangitis may be difficult in the absence of a clear history or of microfilariae in the blood In most cases the general reaction and local signs are less severe than in acute bacterial lymphangitis The local glands are also less tender than during bacterial infection The absence of any focus of infection may suggest a wider search The centrifugal development of the lymphangitis, and focal points of intense tenderness and possibly abscess formation along the course of the inflamed lymph vessel are suggestive of filariasis

Acute filarial funiculitis, orchitis and epididymitis may be indistinguishable from the results of gonococcal infection, which may be coexistent In uncomplicated filarial inflammation there is no urethral discharge The history of repeated attacks, the thickened cord, the frequent involvement of local glands, and the development of hydrocoele are all suggestive of filariasis

In an endemic area varicose superficial and deep lymphatics, especially in the femoral or scrotal region, and hydrocoele should be regarded as filarial in origin unless proved otherwise By this stage the microfilariae may usually be found in the blood

Elephantoid tissue changes appearing in an endemic area, especially in native inhabitants, are almost always filarial in origin In the early stages of elephantiasis oedema of a limb, especially when unilateral and associated with enlargement of local lymph glands, should be regarded with suspicion

A moderate eosinophilia develops in the early stages of the disease and persists into the late stages

LABORATORY DIAGNOSIS

The certain diagnosis of filarial infection can be made only by demonstrating the presence of the worm This can be done most easily by finding the microfilariae in the blood Occasionally, the adults may be found in lymph glands excised for the purpose, or by X-ray when calcified Biopsy of lymph glands is not a wise procedure, however, since it may further interfere with the already impeded drainage of lymph from the affected area The identification of adult worms should be left to the expert. Some indication of the species being dealt with may often be obtained from knowledge of the likely breeding grounds of the vectors The presence of pools containing *Pistia* plants, for instance, is suggestive of possible malayan infection

Microfilariae are found in the blood in the intermediate stages of the disease They are absent in the very early and late stages. They must be looked for at the right time. If the prevailing worm produces perio-

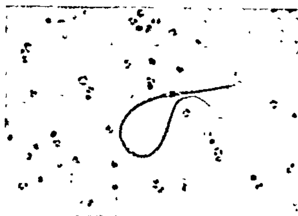


Fig 9 Microfilaria of *W. bancrofti* in a stained thick blood film taken at night. [Courtesy Professor W E Kershaw]

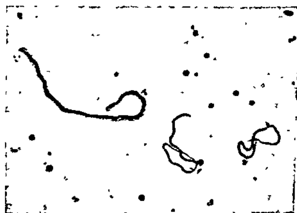


Fig 10 Microfilaria of *L loa* and *A perstans* in stained thick blood film taken during the day
[Courtesy Professor W E Kershaw]

dic microfilariae, the blood should be examined somewhere about midnight. If the microfilariae are relatively aperiodic, the blood is often best examined in the early afternoon, although microfilariae are usually present throughout the day.

The numbers of microfilariae found in the blood vary enormously and may be very great

Blood is examined by taking six or more thick films as for malaria Field's stain may stain the microfilariae well enough to make the

TABLE I

THE DIAGNOSIS OF MICROFILARIAE

MICROFILARIAE PRESENT IN BLOOD			
Sheathed and large	graceful, discrete nuclei, tail tip free of nuclei	plentiful at night rare during day	mf of *W bancrofti*
		present during day and night	mf of *W bancrofti* (*W pacifica*)
	irregular, heavy nuclei	plentiful during day, rare at night, long thin tail very tapering nuclei to tip	mf of *L loa*
		plentiful at night, rare during day, tail long 2 small round nuclei separated by 2 long spaces from body nuclei	mf of *B malayi*
Unsheathed and small	bulbous nucleus at tail,		mf of *A perstans*[1]
	pointed tail with nuclei not to tip		mf of *M ozzardi*[1]
MICROFILARIAE PRESENT IN SKIN SNIPS			
Head spatulate, tail sharply pointed tip no nuclei			mf of *O volvulus*
Head cylindrical, tail curved sharply at tip nuclei to tip			mf of *A streptocerca*[1]

[1] Regarded as of no clinical importance

differentiation of species possible but it is better to stain with haemalum [1]

Microfilariae may be distinguished by their appearance and the arrangement of their body nuclei Expert advice is useful in this identification (See Tables I and II)

[1] *Thick blood films* [illegible]

TABLE II

GEOGRAPHICAL DISTRIBUTION OF MICROFILARIAE

Area	*B. bancrofti*	*W. malayi*	*W. pacifica*	*L. loa*	*O. volvulus*	*A. perstans*[1]	*A. streptocerca*[1]	*M. ozzardi*[1]
West and Central Africa	+	−	−	+	+	+	+	−
East Africa	+	−	−	−	+	+	−	−
Mediterranean	+	−	−	−	−	+	−	−
Central and South America	+	−	−	−	+	+	−	+
India, Ceylon, Asia Islands excluding Oceania	+	+	−	−	−	rare	−	−
Oceania	+	+	+	−	−	rare	−	−

\+ = present
− = absent

[1] Regarded as of no clinical importance.

If microfilariae are not found by examination of thick blood films in a suspected case, various methods of concentration of the blood specimens may be employed Such techniques are best left to those accustomed to them Knott's method consists in taking 1 ml venous blood into 8 ml of 2 per cent formalin solution in distilled water The mixture is centrifuged for five minutes and the deposit examined for dead microfilariae, which may be present in enormous numbers

Fresh coverslip preparations of blood may also be examined at the same time as the dried stained specimens The microfilariae are actively motile and may be seen swimming about agitating the erythrocytes This form of examination is unreliable and should never be used without stained films

Microfilariae may be found in the fluid obtained from varices, from hydrocoele sacs, and sometimes in ascitic and pleural accumulations of fluid and even in joint fluid during synovitis They are usually present in the sediment of the milky urine passed during chyluria, their absence from the urine in this complication does not exclude the diagnosis

OTHER DIAGNOSTIC METHODS

Acute allergic responses arising during the first few days of a course of hetrazan are of significant import in the diagnosis of suspected filarial infections

Complement fixation tests have been devised in which the antigen is made from an alcoholic extract of the dog heart worm *Dirofilaria immitis* or from microfilariae or adults of *W bancrofti* The serum of the patient is tested in a reaction similar to the Wasserman reaction A positive reaction is an indication of present or past infection

Skin sensitivity tests with similar antigens have also been used, and may be helpful in difficult cases, or in late cases of elephantiasis in which microfilariae cannot be found The antigen is injected intradermally near a control injection of saline and after an interval of 10 to 15 minutes the resulting wheal is measured and compared with the control Details for this test vary according to the antigen used and should be consulted before the method is employed

The skin test is the more reliable, but the development of occasional false positives sometimes makes interpretation difficult

TREATMENT

The treatment of filariasis is local and general

If the patient is febrile he should be nursed in bed in the acute stages he should be taken off all duties Inflamed parts should be rested as much as possible A suspensory bandage is necessary in epididymitis and orchitis and in lymph scrotum The application of heat may exacerbate the condition

Oedema in a limb should be treated by rest and, in the leg, by elevation and firm bandaging from below up

The oedema in the early stages of elephantiasis in the leg may be relieved by firm bandaging, preferably after a period of rest and elevation The bandage is started on the foot and continued upwards to the knee or higher Sorbo rubber strips may be placed against the skin before bandaging Such treatment is purely symptomatic and helps the patient carry on his work; it does not affect the course of the condition

Secondary infection through the skin in elephantiasis can be avoided to some extent by keeping the affected part clean by frequent washing and drying The skin in lymph scrotum is particularly liable to infection and must be carefully protected

Surgical procedures are helpful in certain conditions, notably hydrocoele, lymph scrotum and elephantiasis of the scrotum. No surgical procedure should be carried out until existing sepsis has been controlled.

Hydrocoele sacs should be removed together with local lymph varices Lymph scrotum and elephantiasis of the scrotum are treated by suspension or removal of the affected tissue after secondary sepsis has been dealt with In operation involving the scrotum care must be taken not to cut the cords or damage the testes, which are usually functional and which are tied down to the posterior aspect of the tumour It is the common practice to implant them in the medial aspects of the corresponding thighs Details of surgical procedures must be sought in the appropriate texts

Chronic discharging sinuses may need radical excision

The prognosis after surgical removal of the scrotum is usually very favourable Attempts to remove strips of elephantoid tissue from the legs have not been so successful Fat embolus and fatal vascular collapse have followed such operations, and there is sometimes considerable difficulty in closing the skin incisions Elephantoid tissue arising from the trunk may sometimes be removed *in toto* by section of the pedicle

Chyluria does not usually require treatment other than rest

A very important aspect of treatment, especially in visitors (such as service personnel) to endemic areas who have become infected after relatively short exposure, is the psychological handling of the case Such patients should be assured that the likelihood of elephantiasis, sterility or impotence is remote

CHEMOTHERAPY

Sulphonamides and antibiotics are helpful only for the relief of secondary infections Temporary diminution in numbers of microfilariae in the blood stream may result from the use of a number of drugs including certain trivalent antimonials, such as sodium or potassium antimonyl tartrate, anthiomaline and fouadin, and pentavalent

antimonials including neostibosan and urea stibamine which are believed to kill some of the adults Organic arsenicals of various kinds have also been tried with poor or equivocal results

The most active drug available at present is hetrazan (banocide, [illegible]

febrile reaction during the first three or four days of therapy

Indirect toxic effects may be severe There may be local inflammatory reactions in the cord and testis, and generalized urticaria and oedema, especially of the face These reactions seldom last for longer [illegible]

The long term results of treatment with hetrazan are good Since it has apparently little action on the adult except in very large dosage, control of a given infection will probably require repeated therapy at intervals of about a year

Dosage: 2 mgm per kilo body weight given orally thrice daily for 10 to 21 days Children in proportion to body weight

CONTROL

The control of filariasis is largely an entomological matter

The use of hetrazan as a prophylactic in populations in endemic areas in the hope of reducing the transmission rate by controlling the human reservoir has been successfully employed in some endemic areas

ONCHOCERCIASIS

DEFINITION

The so-called blinding filarial disease A condition caused by infection with the nematode *Onchocerca volvulus* transmitted by certain species of *Simulium* flies It is characterized by the development of subcutaneous nodules, pruriginous and other skin changes and ocular lesions which may lead to blindness

GEOGRAPHICAL DISTRIBUTION

Onchocerciasis occurs in localized areas of Central and South America and in many parts of Africa, including Kenya Uganda Tanganyika, Rhodesia, Nyasaland, the southern Sudan Tunis, Senegal, Liberia, Ghana, Nigeria the Cameroons and the Belgian Congo It does not occur in corresponding latitudes of Asia, Indonesia or Australasia.

AETIOLOGY

CAUSATIVE AGENT

Onchocerca volvulus (called *O caecutiens* in America) is a nematode belonging to the Super family Filarioidea. It is related to other nematodes which infect animals including cattle and horses.

Man is the true host and usual reservoir of the infection Recent evidence indicates that the chimpanzee may also become infected and act as a reservoir

Certain species of *Simulium* are the intermediate hosts

In man are found the adults, eggs and microfilariae.

The infective larvae introduced by the fly develop very slowly in the human host, a period of a year or more being necessary before maturity is reached

O volvulus is a filiform white worm with characteristic annular thickening of the cuticle. The females may measure over 50 cm in length and are much longer than the males. Females are ovoviviparous. the uteri of the gravid female are filled with eggs containing larvae in all stages of development.

Adult worms are present in the subcutaneous nodules which form a characteristic feature of the condition They may also very occasionally be found free in the tissue spaces of the host, especially in dense fibrotic tissue

Most nodules contain several worms of both sexes coiled up together in an intricate tangle lying in cystic spaces or in cavities which are incompletely lined with degenerate endothelium

Worms live for years within the nodules, as may be gauged by the recovery of living worms from nodules known to have been present for long periods After death they are frequently calcified

Larvae and eggs are found in large numbers near the coiled gravid female Most eggs contain fully developed larvae

The microfilariae vary greatly in size (150-350 μ) They have slightly bulbous heads and pointed tails The nuclear column does not reach into the head or the tail They are unsheathed

Microfilariae are found in the nodules near the gravid females, in tissue spaces especially just beneath the skin, and occasionally in lymphatic vessels and lymph glands

They are present in the skin over and near the nodules, and often in the conjunctiva They may on occasion be found beneath the skin of any part of the body

They are actively motile and often migrate beneath the skin

Microfilariae are believed to live for a long time in the human host

THE VECTOR

The intermediate development of the worm takes place in certain

species of *Simulium*, small black flies or buffalo gnats measuring about three to four millimetres long Only the females transmit the worm

The most important species of *Simulium* known to transmit the infection are *S. damnosum* (West Africa), *S naevei* (East Africa) and *S ochraceum* (America)

DEVELOPMENT IN THE FLY

Microfilariae are ingested during a blood feed Those that escape from the insect's stomach into its tissues within 24 hours develop in the thoracic muscles and after a series of ecdyses become converted into infective larvae which reach the proboscis and enter the human host during the insect's bite

The development in the fly takes about a fortnight It requires suitable conditions, including the right range of external temperature (about 50 to 90° F)

TRANSMISSION

Recent work indicates that the fly may become infected after biting skin areas involved in early or well-developed lesions, but not in late 'burnt-out' lesions in which the few remaining larvae are too deep in the corium for the fly to reach

The factors governing the infectivity of *Simulium* are not clearly understood The degree of infectivity of flies and the rate of transmission vary sharply from area to area In most endemic areas where the infected human host is exposed to biting, the infectivity rate in the flies is high Occasionally, however, it has been found that the usual vector is present and apparently uninfected whereas a less common species is heavily infected

On the whole, however, transmission of the disease occurs where the common vectors and infective human hosts are present simultaneously The distribution of the disease is thus largely controlled by the ecology of the fly

Simulium requires hot moist shady conditions for breeding The larvae become attached to stones or vegetation or sometimes crustaceae in fast-running, well-aerated water and are thus especially frequent during rainy seasons, often in streams running over rocks which are dry and exposed in the dry seasons

Details of breeding depend on the locality

In Africa it is greatest in the wet seasons Larvae are found in small rapidly running streams in the vicinity of large rivers in undulating country usually above 1000 to 1500 feet The adults rest in shade under leaves or in grass very near the breeding grounds They seldom fly more than a few feet from the stream in dry and sunny weather, but may wander several hundred feet in cloudy moist conditions If dis-

turbed they bite at any time of day, especially in the afternoon. Biting occurs most frequently on the legs below the knee. Fishermen and others with occupations associated with the breeding streams are thus particularly liable to infection. Local reactions to the bite are vigorous.

In America breeding continues on a large scale the whole year round in damp virgin forests lying between 2000 and 4500 feet above sea level. It is maximal during the rains, i.e. between September and February. Similar conditions to those in Africa are required, including fast-running, well-aerated streams. The adult flies leave the forests for the local coffee plantations where they shelter in the shade of leaves or in the grass. Biting is probably more frequent on the upper part of the body in these conditions than it is in Africa.

GENERAL

Infection probably occurs at any age. Nodules have been observed in children under the age of 1 year, but begin to appear more commonly in children of 3 years or more, and in adults. The appearance of the signs of infection is generally very slow, in keeping with the maturation of the worm in the human host.

Either sex may be infected. The relative incidence of lesions in the sexes is largely a matter of chance exposure to infective flies. For instance, in villages set some way from streams and rivers to which the men go daily for fishing, the incidence is much greater in men than women.

There is no racial resistance to infection. The disease is much commoner in the local populations of infective areas than in visitors, but the latter may become infected, especially after long continued exposure.

Intensity of infection is the chief factor in deciding the development of the clinical syndrome. It is measured by counting the number of viable microfilariae observed per mgm of skin removed from appropriate parts of the body.

PATHOLOGY

The lesions of onchocerciasis include the nodules, certain skin changes, and ocular changes. The nodules arise directly from the presence of the adult worms. Opinion is divided concerning the pathogenesis of other lesions, but it is generally agreed that microfilariae, possibly only when dead, must play an important role in them. There is also an allergic factor.

NODULES

Nodules may contain living or dead adults. In the developmental stages of the tumour the worms are always alive.

Nodules develop in subcutaneous tissue, especially near bony structures They consist essentially of a fibrous capsule within which lies a mass of coiled worms of both sexes surrounded by an avascular fibrous inflammatory tissue of varying degrees of cellularity. The infiltrating cells are usually lymphocytes and plasma cells, occasionally epithelioid or giant cells may be present There are large numbers of eosinophils Polymorphs are present in large numbers only after heavy secondary infection has taken place

On section the tumour is usually whitish yellow and contains a hard spongy mass consisting of cellular fibrous tissue honeycombed with sections of worms, together with eggs and microfilariae Occasionally the central mass may be soft and pultaceous, in late lesions the worms may be calcified.

The skin over the nodules usually contains numbers of active microfilariae, the numbers falling as the distance from the tumour increases There may be no other epidermal change, but occasionally there is some oedema and slight general and perivascular infiltration with lymphocytes, plasma cells and eosinophils.

SKIN LESIONS

In many parts of the body the microfilariae may be found immediately beneath the skin epithelium, without any local reaction in the tissues In other areas there may be some thickening of the epithelial layers, especially the horny layer, associated with reduction in numbers of sweat and sebaceous glands A mild degree of cellular infiltration of the subdermal tissues, and some perivascular infiltration of local vessels is common, together with some congestion and dilatation of vessels and lymphatics There may be some oedema Acute inflammatory changes may arise from secondary infection subsequent to pruritis and scratching

Changes in the skin are usually associated with the presence of microfilariae but the latter are not always present It has been suggested that in the absence of microfilariae certain lesions may be allergic in origin; some confirmation of this has been offered by the observation that reactions to filarial antigens are more vigorous in individuals subject to pruriginous changes in the skin

The distribution of lesions and microfilariae in the body in a given case depends on the intensity of the infection and the site of the original biting In Africa serial skin snips taken from selected areas have shown that lesions and microfilariae are concentrated in the region of the calf and hip and to a lesser degree in the thighs and legs The upper parts of the body are affected only in relatively heavy infections The distribution in American onchocerciasis is said to be the reverse of this, the upper half of the body including the eyes being most affected

OCULAR LESIONS

Microfilariae have been found in most parts of the eye except the lens and the retina. In some regions they are particularly common in the cornea, and uveal tract. Blindness may result from corneal opacities, choroidoretinal degeneration, secondary cataract and optic atrophy.

The conjunctiva often contains large numbers of active microfilariae, usually with little or no tissue reaction After some time inflammatory infiltration develops (probably about dead microfilariae) and the whole tissue thickens and becomes irregularly pigmented.

Living microfilariae do not apparently damage the cornea. Opacities develop around dead microfilariae and consist of lymphocytes and plasma cells grouped round the body *of the larva which lies stretched* out horizontally These areas of reaction tend to clear spontaneously in the early stages but later may become permanent and confluent The lesions in the cornea develop in the substantia propria between Bowman's and Descemet's membranes The epithelium is unaffected until the late stages during which there may be some degenerative changes and accompanying vascularization Ulceration results only from secondary sepsis There may be considerable folding and some pigmentation of Descemet's membrane

The anterior chamber often contains large numbers of microfilariae. A brownish mass of dead microfilariae slowly deposits at the bottom of the chamber, engendering a mild inflammatory reaction The obstruction caused by this mass sometimes leads to glucoma. Distortion of the pupil arises from involvement of the iris in the inflammatory processes proceeding in the anterior chamber. There is generalized loss of iris pigment which tends to clump and become absorbed on Descemet's membrane and in the mass in the anterior chamber. The ciliary body undergoes a similar low grade inflammation, microfilariae are sometimes present in large numbers The cyclitis produced may give rise to secondary cataract and glaucoma Microfilariae have not been found *in the lens They occasionally appear in the vitreous, which, however,* remains clear

Certain changes in the retina, including narrowing of the vessels, irregular clumping of pigment, atrophic choroiditis and sometimes optic atrophy with complete loss of vision, are widely believed to result from onchocercal infection, but there is at present some division of opinion as to their origin. It has been suggested, *for* instance, that they may in fact be hereditary retinopathies entirely unrelated to the infection

CLINICAL PICTURE

Onchocerciasis develops slowly as the worms mature The period of time necessary for the full maturity of the adult is not certainly known

but nodules have been reported in children less than one year old In most cases, however, the period is considerably longer It is uncommon to find nodules in children before the age of three After this they be-

early always seen in the
are more often seen in
visitors The latter may exhibit occasional fever and transient urticarial pruriginous skin reactions limited to areas of the face and trunk These lesions resolve with the appearance of the more permanent signs of infection

The commonest first indication of infection is probably the development of subcutaneous nodules, followed by the appearance of skin lesions In some regions, however, the latter appear and may become extensive before, or sometimes in the absence of palpable nodules

Eye lesions appear late and are thus uncommon in very young children and commoner in adults with a long history of nodular or skin lesions They may develop without obvious intervening nodular or skin stages They are rare in non-indigenous cases

NODULES

Nodules first appear as small tumours beneath the skin, gradually developing to full size over the course of three or four years They vary greatly in size Some may be as small as 2 or 3 mm across, others as much as 60 mm Some are too deeply situated for palpation

The nodules are firm and not tender In the quiescent stage the skin moves freely over them In some areas they are loosely attached to the bone below, especially on the skull, where they may be bound to the periosteum and in the course of time come to lie in a shallow depression

The nodules *are usually very obvious, well raised above the general* surface of the skin, and sometimes pedunculated, especially in the groin or near joints

They tend to remain quiescent for years, and normally cause the patient little trouble unless they become secondarily infected Occasionally, however, there may be a mild inflammatory episode, lasting a few days in which the tumour enlarges and becomes tender, and the overlying skin becomes erythematous and oedematous These inflammatory changes are most often seen in tumours in the neighbourhood of large joints

The number of nodules varies enormously from patient to patient and from region to region In the individual there may be only one, or many of varying sizes In one district it may be common to find multiple nodules, in another none or only a few In parts of West Africa, for instance, the number in a given patient varies from 1 to 20, in certain areas of East Africa it is common to find 30 or more, some-

times over a hundred; in America there are usually only a few. In some areas it is common to find extensive skin lesions with few or no nodules

The distribution on the body is equally uneven In Mexico and Guatemala nodules are found almost always in the head, particularly in the scalp, and there are few on the trunk In many parts of Africa, they are rarely found on the head and are commonest on the trunk,



Fig 11 Onchocercal nodules over trochanters and elbows

in the lateral intercostal spaces, in the axillae, in the pelvic region or in association with joints, especially the elbow and knee. In some areas in East Africa they are found commonly on the head and also on the trunk

There is no good explanation of the location of the tumours It is believed that some arise at points where there is a confluence of lymphatic vessels, or where some obstruction to lymphatic flow arises as a result of pressure, for example, from head [illegible] l that the [illegible]

often

Wh[illegible] multiple they often appear in circumscribed groups of half a dozen or more scattered unevenly over the trunk Lesions on the scalp often occur in groups of two or three

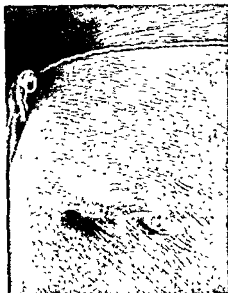


Fig 12 Same patient
Note nodules on buttock and changes in the skin texture
[Courtesy of Annals of Tropical Medicine and Parasitology, Liverpool
Photographs by Professor D B Blacklock]

SKIN LESIONS

The appearance of nodules is followed or preceded in most cases by changes in the skin which develop insidiously and may become very disturbing to the patient

surrounding skin There may be desquamation of the horny layers These areas are intensely itchy and may cause insomnia, secondary infection often arises from constant scratching

In very heavy infections the xerodermatous changes affect the face and ears, in which dense irregular swellings develop Microfilariae are usually present in the superficial layers of the corium in early lesions and deeper in later more developed lesions Old lesions are often referred to as 'burnt out' In them the skin is thin and depigmented in

patches. The elasticity is gone and the microfilariae are found only in the deep layers of the corium. This type of lesion is no longer infective



Fig. 13 Changes in the skin in Onchocerciasis
(Note nodule over ribs)

American onchocerciasis gives rise to somewhat similar changes in the skin which have been given special names from time to time The distribution of lesions and microfilariae is from above downwards, unlike the African form of the disease Thus, the most advanced lesions and the nodules are found on the head, neck, shoulders and upper arms and trunk. Hard oedema of the neck and face, including the eyelids and sometimes the ears has often been described. This oedema is accompanied by some lymphocytic infiltration and in the early stages may give the skin a hard glossy appearance. Urticaria is sometimes also

present. In white skins a greenish tinge has been observed in the affected skin, giving rise to the local name of *mal morado*. These lesions are often extremely itchy and frequently infected from scratching.

'Coast erysipelas' has been described as a complication of American onchocerciasis but is now considered to be primarily streptococcal in origin. The patient suffers from hard oedema of the face, sometimes involving the lips and eyelids. The skin is tense, oedematous and painful and there is a severe general reaction with high fever. Similar lesions have been described on the limbs.

It is often difficult to distinguish onchocercal skin lesions from the effects of secondary infection, the presence of other infestations such as scabies, or the effects of deficiencies. Nevertheless, there is ample evidence to indicate that the pruriginous and xerodermatous lesions described above are related to the worm infection.

OCULAR LESIONS

The incidence of eye lesions in endemic onchocerciasis varies con-

in some parts of Africa, but in others the incidence of eye lesions is low and that of blindness very small. The latter is particularly so in districts of Sierra Leone, for example, in which nodules are rarely found in the head and eye lesions are uncommon. In Ghana the incidence of eye lesions varies. In some areas in the north it is as high as 10 to 20 per cent of those infected.

In general, ocular changes appear most commonly in individuals with nodules on the head, but they may occur in the absence of nodules.

In the ordinary course of events ocular lesions develop late. An interval of years usually elapses between the appearance of the first nodules and the beginning of changes in the eyes. This interval is believed to be controlled to some extent by the age and general condition of the patient and the presence or absence of nodules near the eyes.

The more advanced eye lesions are commonly found only in middle-aged or older individuals. They have occasionally been reported in children under five years of age.

The development of ocular lesions in African onchocerciasis may follow a steadily progressive pattern, the early stages of which are so mild as to be often overlooked. In the American disease the onset may be more rapid, and is accompanied by local pain which is persistent during the hours of sunlight. There is first a mild chronic conjunctivitis subject to exacerbations with gradual thickening and some pigmentation of the conjunctiva with little or no infection. Corneal opacities

ment may appear. Vascularization of the conjunctiva such as is seen in infective conjunctivitis is not, however, a feature of the condition except in the late stages. Lesions of the anterior chamber, iris and ciliary body may continue to develop insidiously, with very little pain or discomfort but with increasing deficiency of vision In the course of five to ten years blindness may result, especially in the presence of secondary infection or trachoma, from opacity, secondary cataract or glaucoma Uncomplicated anterior eye lesions probably do not often lead to blindness

In many cases of onchocerciasis, even when there are no nodules in the head, microfilariae are present in considerable numbers in the conjunctiva Changes similar to those in the skin may or may not be present in the early stages, but as the condition develops, mild cellular infiltration of the superficial tissues occurs and there may be some

develops affecting mainly the interpalpebral area especially on the nasal side but often involving also the pupillary area The opacities develop as tiny rounded grey areas with ill-defined margins; many may develop and ultimately become confluent; producing a characteristic 'frosted glass' appearance. Even at this stage there is very little vascularization unless secondary infection is present Pannus when present usually develops on the inferior segment in contrast to that in trachoma The cornea does not ulcerate in the absence of infection

With a slit lamp microfilariae may often be seen in the aqueous, sometimes singly, sometimes in groups Dead microfilariae may accumulate in the course of time in the bottom of the anterior chamber to form a brown-grey mass which later becomes involved in progressive slow inflammatory changes which include the iris The most characteristic early change in the latter is generalized loss of pigment, especially from the inner margin of the iris producing the so-called spongy 'pumice-stone' effect. Pigment occurs in scattered clumps in the iris, in spots on the corneal endothelium or on the adjacent lens surface Pigment may also be mixed with the mass of dead microfilariae and inflammatory tissue involving the floor of the chamber The iris be-

changes in the iris are the absence of acute general inflammation and the peculiar lack of severe symptoms Similar changes in American

onchocerciasis have been associated with intense pain, which may arise from complications, such as glaucoma Cyclitis of a similar mild asymptomatic type commonly follows the iritis and leads to serious complications, particularly secondary cataract

Glaucoma, with ultimate optic atrophy, may result from either cyclitis or obstruction in the anterior chamber arising from the low grade inflammatory changes described above

The lens does not harbour microfilariae Nevertheless, cataract is common, presumably following degenerative changes in the ciliary body Microfilariae have been seen in the vitreous and may cause some opacities It is not known how significant these are

In some geographical areas changes in the fundus have been observed in individuals with heavy infections or with extensive 'burnt-out' skin lesions

Microfilariae have not been identified in the living retina, but have been observed occasionally in enucleated eyes

The retina may show one or more areas of degenerative changes which may extend to the disc margin and are roughly circular and fairly well demarcated from the normal area Within these lesions the retina is abnormally transparent and the pigment is collected centrally in one or two masses; the background has been described as resembling 'cracked sun-baked mud' Small aggregations of pigment lying over the vessels may be present in the otherwise normal retinal fields There is commonly atrophic choroiditis The choroidoretinal changes are accompanied by some degree of optic nerve atrophy, with well-defined disc margins

Retinal changes may be associated with lesions in the anterior eye It is important to note, however, that in some regions it is common to find cases with extensive retinal damage and little or no change in the rest of the eye beyond minor lesions in the iris or cornea Cases of the latter type may have no palpable subcutaneous nodules, but there are nearly always extensive skin changes

Individuals with well developed retinal changes are usually completely blind There remains some doubt about the cause of these retinal lesions Some observers relate them directly to the onchocercal infection

possible to assess fully the importance of onchocerciasis as a blinding agent

OTHER COMPLICATIONS

Elephantiasis similar to, but milder than that resulting from infection with *W bancrofti* and *B malayi* is believed to develop occasionally in

onchocercal infections. The oedematous skin changes are less pronounced than in the other filarioid infections, and appear most commonly in the scrotum and in the leg below the knee. Onchocercal lymph scrotum and hydrocoele are not uncommon; the fluid contains identifiable microfilariae.

There is normally a considerable eosinophilia in established cases. Occasional very high counts of eosinophils have been recorded.

COURSE AND PROGNOSIS

Onchocerciasis is a progressive condition which causes little harm to the patient unless the eyes are involved In the latter event the prognosis for vision may be unfavourable

DIAGNOSIS

It may be difficult clinically to distinguish between an onchocercal nodule and a fibroma, lipoma or enlarged lymph gland Nodules may sometimes be mistaken for the juxta-articular nodules of yaws.

Diagnosis is made by excision for histological examination and identification of the worm, or by aspirating fluid from the nodule and identifying the microfilariae and eggs. Fluid aspirated from a nodule will usually contain eggs and microfilariae but their absence is not absolute evidence of a negative diagnosis, since a tumour may be completely fibrosed or occasionally carry worms of the same sex or even only one worm.

Microfilariae should also be identified by examination of skin or conjunctival snips They may be found most easily in samples of skin taken from the region of a nodule. The skin is lifted (by inserting a needle beneath it or squeezing it firmly between the finger and thumb of one hand) and cleaned with alcohol; a fine shaving is then removed [illegible]

the conjunctiva is unnecessary for repair

In most cases of ocular onchocerciasis microfilariae are to be found in large numbers in the bulbar conjunctiva. A slit lamp is necessary to identify them in the anterior chamber of the eye They are best looked for in the inferonasal quadrant

Differentiation of the microfilariae from others sometimes found in the skin requires stained preparations (See pp 87-9)

OTHER DIAGNOSTIC METHODS

Complement fixation and intradermal tests have been devised using antigens made from *O volvulus* The results are equivocal, owing to the high proportion of positive reactions in control cases

TREATMENT

SURGICAL EXCISION OF THE NODULES

Where it is practicable an attempt may be made to remove all identifiable nodules Successful excision of nodules eliminates at any rate the great bulk of adult worms and may eventually lead to improvement in skin and ocular lesions or at least to the retardation of the progress of the latter

CHEMOTHERAPY

Two drugs are at present used with some success, i e antrypol (suramin, germanin) and hetrazan

(i) *Antrypol* This drug is also used extensively in the treatment of trypanosomiasis (see p 403) It causes the disappearance of some microfilariae from the skin and kills at least some of the adults in the nodules.

Dosage For an adult, an initial dose of 0 2 gm, followed by 1 0 gm intravenously once every 5 days for 5 or 6 doses

(ii) *Hetrazan (diethylcarbamazide)* The chief action of this drug is apparently on the microfilariae It is more rapid than antrypol in its action

Dosage In the adult, start with an oral dose of 2 mgm per kilo body weight once a day for the first day, twice a day for the second or third day, and three times a day for the third or fourth and consecutive days for a total of 21 days

Toxicity Both antrypol and hetrazan may be followed by unpleasant effects, including burning and redness of the eyes, pruritis, hard oedema of the face and ears, and sometimes of the limbs, and slight fever The reactions are more severe with hetrazan Antihistaminic drugs partly relieve these reactions, and may be given as a routine

The initial dose of 0 2 gm antrypol is given to test for possible idiosyncracy to the drug, indicated in the first instance by the appearance of proteinuria and casts The [illegible]

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Toxic reactions to hetrazan commonly appear after the first few doses These reactions are largely allergic and may be controlled by giving standard doses of antihistaminic drugs for the first four to five days of treatment

PROPHYLAXIS

The control of the vector is a difficult entomological problem which has its own special aspects in different localities. The elimination of *Simulium* flies is the ultimate objective.

Protection against biting is afforded in some degree by means of protective clothing designed to protect the lower legs, and by use of repellents

LOIASIS

DEFINITION

An infestation with the filarial worm *Loa loa*, transmitted by species of *Chrysops* flies The condition is confined to certain regions of tropical Africa and characterized clinically by fugitive or 'Calabar' subcutaneous swellings

GEOGRAPHICAL DISTRIBUTION

Loiasis is found in equatorial rain forests and on their fringes across a narrow band of territory stretching roughly from latitude 10° N to 5 S from the shores of the Gulf of Guinea to the Great Lakes.

Within this area the distribution is very irregular Areas of intense infection occur in parts of eastern Nigeria, the Cameroons and the Belgian Congo.

AETIOLOGY

THE CAUSATIVE AGENT

Loiasis results from infection with *Loa loa*, a filarial worm the adults of which are shorter and thicker than *W. bancrofti* and exhibit rounded bosses on an otherwise smooth cuticle. The female is about twice the length of the male. The uterus of the female usually contains masses of ova containing embryos in all stages of development

Both sexes are found in man in the connective tissues They are found singly, never *in copula* Maturation in the host tissues takes about 12 months in most cases; periods as short as 6 months and as long as 9 or 10 years have been reported

Little is known of the life history of the worm in the human host It is not known where fertilization and larviposition take place

The adults wander about the tissues usually in the soft tissue planes and cause little direct reaction on the part of the host. From time to time they appear beneath the skin in various parts of the body, especially where the connective tissue is loosely knit.

For practical purposes man may be regarded as the only reservoir It is possible that in some regions monkeys may act as reservoirs

Most subjects in whom adults have been identified will be found to carry microfilariae also, but there are some in whom the latter cannot be found even after the most exhaustive search It is not known whether in these individuals there has been unisexual infection or failure of fertilization or whether larviposition has occurred in some reservoir organ and the numbers in the blood are too small for detection

The actively motile microfilariae are commonly present in the blood They are sheathed and vary in size considerably, the largest being about the same size as those of *W bancrofti* (280-300 μ) (See pp 87-9)

Microfilariae are rarely found elsewhere than in the blood or within gravid females They have occasionally been recovered from lymphatic glands They are found in greater numbers during the day than during the night There is great variation, however, in this diurnal periodicity not only from patient to patient, but in the same patient from time to time They are commonly in greatest concentration about midday

THE VECTOR

The distribution of the genus *Chrysops* is considerably wider than that of the disease The species responsible for transmission, however, are those found only within and at the edge of the equatorial rain forest, namely *C silacea*, *C dimidiata* and *C distinctipennis* Only females are concerned in transmission

Infective microfilariae are ingested by *Chrysops* while feeding on the human host The larvae pass from the stomach of the insect to the thoracic muscles and eventually present in the proboscis as the infective form by the 10-12th day after feeding The flies are usually free of infective forms by the 17th day

Chrysops breeds in densely shaded slowly running streams or stagnant pools where the bottom is sandy but covered by mud and decaying vegetation The adults normally live high in the canopy of the forests but are attracted by movement in open spaces especially when the latter are on high ground roughly level with the canopy, or in rubber plantations in which there is no cover crop In such situations adults may be found in abundance They bite freely in shade chiefly in the hours between 8 30 a m and 5 p m , but not in darkness or in direct sunlight There is some evidence that the flies prefer to bite dark skin They bite freely on the bare skin and can penetrate loose-knit clothing

There is sometimes a severe local reaction to the bite but this is of very irregular occurrence and though it has been suggested that the development or otherwise of local reactions depends largely on whether infective larvae are introduced at the bite, it may depend on the previous sensitization of the patient to the bite of the fly

The mode of entry of the infective larvae during the bite of the fly is

not known. It is most likely that they are introduced through the wound made during feeding.

GENERAL

All races seem to be susceptible to loiasis. The condition appears more commonly in adults than in children, possibly because of the slow maturation of the worms. Males are more commonly infected than females in some areas, probably owing to differences in occupation. In highly endemic regions practically the whole adult population is probably infected.

PATHOLOGY

Adult worms apparently circulate freely in the connective tissue without usually causing local tissue reactions. They may for instance be found accidentally during surgical operation, sometimes in considerable numbers.

The Calabar swelling consists mainly of oedematous tissue in which the adult worm may or may not be present. In the more persistent swellings there may be some lymphocytic infiltration of the connective and perivascular tissues. The origin of these swellings is not understood. Many authorities regard them as local sensitivity responses to the recent presence of the adult worm. Similar tumours have been produced by the injection of antigens made from the filarial worm of the dog into the subcutaneous tissues of known sufferers from loiasis and bancroftian filariasis.

CLINICAL PICTURE

In many subjects infected with *Loa loa* pathogenic signs and symptoms may never appear, or may be so trivial as to escape notice. In [illegible]

It is not clear what determines the individual reaction to the infection, the intensity of the original infection or repeated reinfections may be significant and it is possible that some have a peculiar susceptibility to light infections.

The clinical effects are mainly related to the appearance of the characteristic Calabar swellings or to the constant migration of the adult worms. The microfilariae in the blood are not believed to be concerned in the clinical picture.

CALABAR SWELLINGS

These may appear as early as three months after infection; they more commonly develop after a year or more and may reappear from time

to time for many years It is common to find only one swelling at any one time but there may occasionally be two or three

The swellings are essentially caused by the development of localized subcutaneous oedema The onset may be preceded for an hour or two by sharp local pain and itching after which the swelling appears within an hour or so and diffuses rapidly, usually becoming several inches across It remains this size for several days and subsides slowly Occasionally a tumour may last a week or several weeks, particularly

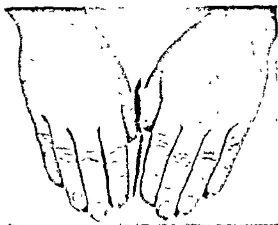


Fig 14 Calabar swelling
[Courtesy Professor W E Kershaw]

in areas exposed to frequent trauma Individual tumours usually arise and subside in the same anatomical area but occasionally they migrate slowly, moving several inches before completely disappearing In some individuals the swellings tend to recur in particular parts of the body, especially near certain joints such as the wrist or knee In others the appearance of the tumours both in time and position seems to be entirely fortuitous, although there is often a history of some mild local trauma shortly before the appearance of the swelling

The patient may suffer from Calabar swellings at infrequent intervals or there may be bursts of them, as many as six or seven following one another inside a month

The swellings may appear anywhere on the body but are especially common in areas open to trauma, including the orbit the lower limbs and the hands The skin over the tumour is not much affected by oedema as a rule, it may be a little reddened and is frequently very itchy and hyperaesthetic Sometimes the Calabar swelling may be

preceded by a localized macular or urticarial rash over or near the area subsequently swollen.

The tumour may cause great pain and discomfort especially if it appears in regions in which the subcutaneous tissue is firm Where the latter is loose and free there may be little or no discomfort. Trauma in

results, which may temporarily incapacitate the patient. The swellings tend to persist around joints for longer than in other areas because of trauma produced by attempts at movement and may sometimes last for weeks, during which the patient suffers severe pain and inconvenience

factor in

condition

particularly in endemic districts in which work has to be carried on by labour imported from relatively free areas.

Swellings, especially in the eyelids, sometimes follow rapidly on the appearance of an adult worm in the local subcutaneous tissues A blow over the region occupied by an adult may also be followed by a local swelling In most instances, however, there is no evidence of the presence of the adult worm at the time of onset of the tumour.

Calabar swellings are not commonly accompanied by any general reaction The eosinophil count is usually high in loiasis, counts as high as 80 per cent have been recorded It varies greatly from time to time in the individual

In some early cases irregular local erythematous patches may appear almost anywhere on the body, these are sometimes followed by local relatively persistent oedematous swellings

EFFECTS OF MIGRATION OF ADULTS

Adult worms are observed from time to time moving actively in the subcutaneous tissues, especially in areas in which the tissues are loose, for example, the breast, the frenum of the tongue, the eyelids, conjunctiva, penis and scrotum In these areas the worm can often be seen very clearly beneath the skin, moving rapidly with an undulant move-

times be attracted to the surface by heat and are said to move away from cold. In temperate climates the adults tend to appear more frequently in the warmer weather.

The movement of the worm across the conjunctiva results in one of

the most irritating and characteristic features of the condition The

[illegible]

be followed by rapidly developing conjunctival oedema and injection The eyelid often becomes oedematous and lachrymation is severe Pain and local irritation are sometimes intense The swelling of the lids and conjunctiva lasts several days before subsiding completely. The episode has been described as a feeling of being 'kicked in the eye'

The clinical manifestations of loiasis are usually limited to those described above, namely the Calabar swelling and the occasional reaction to the subcutaneous wanderings of the adult worms and eosinophilia In some cases temporary diffuse oedema of a part or the whole of a limb may develop and last for a few days to a fortnight or longer, such oedema, particularly involving the hand and wrist or the forearm, is commonly seen in some districts It may occur in association with an obvious Calabar swelling, but often arises spontaneously

Other effects reported have included generalized urticaria and oedema in the region of the wandering adult Oedema and erythema of the skin proper seem to be relatively uncommon except as stated above.

DIAGNOSIS

In individuals exposed to infection the appearance of transient subcutaneous swellings is usually diagnostic Many months may elapse between the first appearance of the swellings and the discovery of the adult worm in the eye or microfilariae in the blood Adults may sometimes be observed beneath the skin months or years before microfilariae appear in the blood In light infections the microfilariae may be present in numbers too small for detection by ordinary methods, in others it is possible that larviposition may be confined to reservoir organs in the body without any spill over into the blood stream

The absence of microfilariae from the blood is therefore not necessarily of great diagnostic significance

Nevertheless in many cases microfilariae are found in the peripheral blood They should be looked for during the day, preferably round about midday, they are often present throughout the 24 hours The numbers of microfilariae vary in some cases from hour to hour There may be as many as 600 per 50 cu mm, easily identified in a single thick blood film, on the other hand they may have to be searched for assiduously through many films The harder the observer looks the more likely they are to be found In some cases however, no amount of searching will detect them They may be seen moving freely amongst

the corpuscles in wet preparations in which a drop of blood has been covered by a coverslip For diagnostic purposes, however, dried stained thick blood films are required. The technique is the same as that required for the detection of other microfilariae. (See pp 87-9)

The adult worms can be seen clearly as they wriggle beneath the conjunctiva When they are present there is no question of the diagnosis.

Differential diagnosis of Calabar swelling from the transient oedemas of trypanosomiasis and of other filarial infections may occasionally be difficult, but the history of Calabar swellings and the search for the causative agent should settle the question

In persons with Calabar swellings but no microfilariae in the blood the presence of a high eosinophilia is a constant and valuable diagnostic sign

Skin sensitivity tests using antigen prepared from *Dirofilaria* or from adult *Loa* are useful in diagnosis The same antigens can be used for the detection of complement-fixing antibodies in the serum. (See p 89.)

TREATMENT

Hetrazan (diethylcarbamazine) has considerable effect on the micro-filariae and less on the adults The immediate results of therapy have been promising During treatment the microfilariae have been observed *to disappear within a few days from the peripheral blood and in some* instances dead adults have been removed from subcutaneous tissues Calabar swellings may, however, recur after some months

The immediate reactions to treatment may be violent, and include generalized urticaria and local irritation and oedema in the region of adult worms There may be an associated febrile reaction and it may be necessary to interrupt treatment until the effects have subsided

Dosage· For adults· 2 mgm per kilo body weight, given three times a day, for up to 21 days.

Children are given doses in proportion to their body weight

LOCAL TREATMENT

Adult worms should be aseptically removed if possible when they appear in the conjunctiva Damage to the worm or incomplete removal may result in severe local reactions of eodema and intense pain and sometimes secondary sepsis

Antihistaminic drugs have some effect locally and may relieve itching and swelling after oral administration.

The incapacitating effects of lesions near joints can be relieved only by rest. *If rest is impossible, swellings tend to persist for weeks*

DRACONTIASIS

DEFINITION

Infection with the nematode *Dracunculus medinensis* or guinea worm

GEOGRAPHICAL DISTRIBUTION

Dracontiasis is found scattered over West, Central and East Africa, in the Sudan, Egypt, Arabia, Persia, Afghanistan, Turkey, southern Russia, west, central and southern India, Burma, the Caribbean Islands, and northern South America

In these areas the distribution is very patchy The local incidence may be very high

AETIOLOGY

Causative agent Dracontiasis results from infection with the nematode worm *Dracunculus medinensis* The clinical effects are produced solely by female worms The male has not been observed in the human host

The gravid female is enormous compared with the male, measuring a metre or more in length in contrast to 30 or 40 mm in the case of the male. The cuticle is smooth, the anterior end bluntly rounded, and the body when mature is largely filled with the uterus

The female matures in the connective tissue of the host The gravid female eventually reaches the surface of the host's body The skin ulcerates near the head of the worm and enormous numbers of free-swimming larvae are ejected through prolapsed portions of the uterus whenever the lesion comes into contact with water Larvae do not appear in the host except within the uterus of the worm

The male worm has been identified in laboratory infections of monkeys and dogs with infective material prepared from human cases It is believed to be absorbed shortly after impregnating the female Some authors hold that the female does not always require fertilization in order to produce viable larvae

The intermediate host is the crustacean *Cyclops* which becomes infected by the free swimming larvae liberated by the adult worm These larvae will survive and remain infective for up to six days in clean water and for as long as three weeks in dirty water or liquid mud After ingestion by the intermediate host the larvae become infective to man in 10 to 12 days, provided the water is suitably warm

TRANSMISSION

The human host becomes infected by swallowing water containing infected cyclops The infective larvae are freed unharmed in the gastric juice and escape through the small intestinal wall Subsequent develop-

the corpuscles in wet preparations in which a drop of blood has been covered by a coverslip. For diagnostic purposes, however, dried stained thick blood films are required The technique is the same as that required for the detection of other microfilariae (See pp. 87-9)

The adult worms can be seen clearly as they wriggle beneath the [illegible]

difficult, but the history of Calabar swellings and the search for the causative agent should settle the question.

In persons with Calabar swellings but no microfilariae in the blood the presence of a high eosinophilia is a constant and valuable diagnostic sign

Skin sensitivity tests using antigen prepared from *Dirofilaria* or from adult *Loa* are useful in diagnosis. The same antigens can be used for the detection of complement-fixing antibodies in the serum. (See p. 89)

TREATMENT

Hetrazan (diethylcarbamazine) has considerable effect on the microfilariae and less on the adults. The immediate results of therapy have been promising During treatment the microfilariae have been observed to disappear within a few days from the peripheral blood and in some instances dead adults have been removed from subcutaneous tissues Calabar swellings may, however, recur after some months

The immediate reactions to treatment may be violent, and include generalized urticaria and local irritation and oedema in the region of adult worms There may be an associated febrile reaction and it may be necessary to interrupt treatment until the effects have subsided.

Dosage For adults 2 mgm per kilo body weight, given three times a day, for up to 21 days

Children are given doses in proportion to their body weight.

LOCAL TREATMENT

Adult worms should be aseptically removed if possible when they appear in the conjunctiva Damage to the worm or incomplete removal may result in severe local reactions of eodema and intense pain and sometimes secondary sepsis

Antihistaminic drugs have some effect locally and may relieve itching and swelling after oral administration.

The incapacitating effects of lesions near joints can be relieved only by rest. If rest is impossible, swellings tend to persist for weeks.

If the ulcerated lesion is douched with water a drop of milky fluid wells up in a few seconds. After an interval of about an hour further douching will have the same effect. This fluid contains myriads of active larvae ejected from the uterus in response to the stimulus of water.

Discharge of larvae will continue intermittently whenever the affected part is exposed to water until the worm has discharged its full



Fig. 15. Adult worm in subcutaneous tissues



Fig. 16. Portion of worm extruding from ulcerated papule on ankle. Bleb from second worm over big toe. [Photograph by Dr E. C. Smith]

load of larvae which may take anything up to three weeks. The tissues about the presenting head of the worm frequently become indurated, oedematous, reddened and very tender. Even in the absence of secondary infection walking may be very difficult, and the patient is compelled to give up his work.

In the case not complicated by secondary infection the local lesion will heal completely about a month to six weeks after its appearance.

Secondary infection is, however, the rule and may lead to serious and unpleasant complications.

Occasionally worms never fully mature or may die before they reach the surface. Under these circumstances they are absorbed completely or partly calcified, sometimes leaving a cord-like mass palpable beneath the skin; they may also become secondarily infected and lead to abscess formation so that the first indication of the infestation may be the discovery of fragments of the worm in the abscess contents.

Gravid females which have not yet presented at the surface are

ment takes place in the connective tissues. Full maturity is reached in about a year

Cyclops abounds in standing dirty water, particularly in puddles, ponds, wells, borrow pits and tanks. Infection is especially likely under circumstances in which the same supply of water is used for drinking and washing The step wells of India are notorious examples of such infective localities.

CLINICAL PICTURE

Dracontiasis is rare before the age of 4. After this the incidence steadily increases, to become highest in the young adult.

The incidence is seasonal in many areas especially in India, infection occurring particularly during the dry season. Infection with a single worm *is usual, but multiple infection is not uncommon. There is no* clear racial or other immunity and reinfection is frequent, even in the already infected subjects

The worm gives rise to no clinical signs until near the point of discharge of larvae The active stage of the infection is accompanied by both general and local signs and symptoms

A few hours before the appearance of the worm at the surface of the skin there may develop some local erythema and tenderness over the area in which the pointing is to take place In some cases there may be general effects sometimes of a severe nature, but in the majority the local lesion tends to develop without any general reaction

In severe cases there may be generalized pruritus sometimes accompanied by scattered urticaria There may be nausea, vomiting and watery diarrhoea In some cases dyspnoea may appear and lead to attacks resembling asthma These general reactions vary greatly in intensity and incidence from patient to patient and locality to locality. They subside as a rule by the time the local lesion has ruptured and the ejection of larvae has commenced

LOCAL CHANGES

The gravid female presents somewhere in the legs or feet in over 90 per cent of all cases It may appear elsewhere, especially in the back, *the arms and scrotum. It has been reported in the orbit It may often* be visible or palpable for its whole length in the subcutaneous tissues.

The patient complains of deep-seated stinging pain in the site in which the worm is reaching the surface A papule or group of papules (which later coalesce) forms rapidly and enlarges over the course of one or two days becoming slowly more indurated. The central region becomes raised and eventually forms a vesicle which soon ruptures, leaving a superficial ulcer large enough to admit a probe The head of the worm is often visible within this ulcer.

If the ulcerated lesion is douched with water a drop of milky fluid wells up in a few seconds After an interval of about an hour further douching will have the same effect This fluid contains myriads of active larvae ejected from the uterus in response to the stimulus of water

Discharge of larvae will continue intermittently whenever the affected part is exposed to water until the worm has discharged its full



Fig 15 Adult worm in subcutaneous tissues



Fig 16 Portion of worm extruding from ulcerated papule on ankle Bleb from second worm over big toe [Photograph by Dr F C Smith]

load of larvae which may take anything up to three weeks The tissues about the presenting head of the worm frequently become indurated, oedematous, reddened and very tender Even in the absence of secondary infection walking may be very difficult, and the patient is compelled to give up his work

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Gravid females which have not yet presented at the surface are

occasionally ruptured accidentally, and give rise to aseptic abscesses which are frequently severe and sometimes accompanied by general symptoms

Abscesses in relation to the worms are nearly always the result of secondary infection Such infections may involve deep structures including tendons, the periosteum and bones, and may be accompanied by severe or even fatal septicaemia.

In some areas a large proportion of patients (in some parts of India, over 20 per cent) suffer from joint lesions, varying from painful reddened swellings to advanced pyogenic infections with later fixation and deformity The majority of such lesions occur in the ankles and knees Changes in joints are believed to occur occasionally without secondary infection

The peripheral blood usually shows an increase in eosinophils which may constitute up to 10 per cent of the total leucocytes.

COURSE AND PROGNOSIS

In the absence of secondary infection the worm will continue to discharge larvae if brought into intermittent contact with water. The incident is over when the uterus is finally emptied and the worm either withdraws and is absorbed or becomes extruded to the surface. This may take several weeks. Full healing of the ulcerated area may be expected in about a month to six weeks from the onset

Rapid healing also occurs if the worm is artificially removed without damage Serious effects are produced if it is broken during removal After such rupture and retraction secondary infection is almost inevitable

The most serious consequences arise as the result of secondary infection

DIAGNOSIS

Patients are usually fully alive to their condition from their own experience *The development of the local lesion is characteristic* The head of the worm can sometimes be identified in the uncomplicated local lesions Fragments may be recovered from contents of abscesses Larvae may be seen in fluid exuded after douching the papule with warm water

Intradermal tests with antigens made from adult *D medinensis* have given equivocal results.

TREATMENT

The patient should be rested. If possible the affected part should be elevated

The local lesion should be kept as clean as possible and secondary infection dealt with by standard methods General septicaemia requires sulphonamides or antibiotics

The worm may be extracted or surgically excised

The time-honoured method of extraction probably gives the best results The local lesion is continuously treated with wet compresses until the discharge of embryos stops, which may take one or two days The head of the worm is then identified and tethered with a fine thread which is tied to a small stick about which the worm is gently wound, a little each day, until it is finally withdrawn The process of extraction may take a fortnight or more Care must be taken not to rupture the worm since this accident is almost always followed by sepsis at the point of the break leading to abscess, cellulitis or generalized septicaemia The stick and rolled worm should be kept covered by a sterile dressing and the whole region should be kept clean and as aseptic as possible

Involvement of joints requires especial care It may be necessary to aspirate and immobilize Expert advice is called for

Chemotherapeutic methods relying on the injection of compounds such as phenothiazine into the region occupied by the worm have not proved very effective

PROPHYLAXIS

The successful control of dracontiasis is achieved by providing adequately protected water supplies, and the erection of infection-proof wells Insecticides such as D D T may be useful for controlling *Cyclops*

XII

THE CLINICAL EFFECTS OF EXPOSURE TO HEAT AND LIGHT

EFFECTS OF EXPOSURE TO HEAT

THE effects of heat on the body arise from interference with the heat controlling mechanisms or from disturbances in the electrolyte-water balance and cardiovascular system, or both.

In the former category are the syndromes of heat hyperpyrexia and thermogenic anidrosis, in the latter, heat exhaustion. These syndromes may appear as distinct entities or be associated In the account given below they are treated separately

PHYSIOLOGICAL PRINCIPLES

A short account of the physiological control of body temperature, electrolyte-water balance and the cardiovascular system on exposure to heat is necessary in order to understand the pathogenesis of these conditions and the principles of treatment

Body temperature At any given moment the temperature of the body is determined by the balance that exists between heat production and heat loss In cold or temperate climates, metabolic production of heat is dissipated from the body surface by the physical mechanisms of radiation, convection, and (rarely) conduction Loss is reduced autonomically by peripheral vasoconstriction, and artificially by protective clothing The variations in the blood flow through the skin are regulated by central reflexes initiated by temperature changes in certain skin end organs and in the blood flowing through the hypothalamic areas of the brain

Sweating In ambient temperatures above body heat, radiation and convection are towards the body and the only methods of heat loss are by evaporation of sweat, and (to a much smaller extent) by insensible perspiration through skin and lungs If the maximum heat loss from the body by these mechanisms fails to balance heat gain from radiation, convection, and metabolism, body temperature rises Radiation heat gain may be reduced artificially by protective clothing, but this interferes with evaporation of sweat at skin level.

Sweat is secreted by glands which are under autonomic control It is essentially a hypotonic saline solution Its salt content is of secondary importance except when sweating is excessive. Its primary function is to provide water for surface evaporation and cooling Sweating may be initiated by a rise in temperature of the skin end organs but the

principal stimulus arises from increase in the temperature of the blood passing through the hypothalamic centres Heating of these centres causes panting and sweating, destruction is followed by inhibition of sweating and an uncontrolled rise of body temperature on exposure to heat

long; as exposure continues, the sweating rate falls off Certain drugs including atropine considerably depress sweating

The evaporation of sweat is more efficient in hot dry than in hot moist climates It is facilitated by movement of air at the body surface About one-third of the amount of sweat secreted is usually evaporated on the skin, the rest escaping as drops or soaking into the clothes

Continuous exposure to heat results in acclimatization, effective sweating beginning at a lower body temperature than on first exposure, and the rate of secretion at a given temperature increasing

Water/salt balance The normal balance may be upset in hot climates by the development of deficiencies of water, salt, or both, brought about by inadequate intake, excessive loss, or both Water balance in a hot environment is discussed below

The average healthy individual in a hot climate secretes about 750 to 1000 ml of urine per day Except in extreme dehydration the daily volume does not fall below about 300 ml

For practical purposes, the only electrolyte of consequence in exposure to heat is sodium chloride The concentration of salt in the sweat of a healthy subject in a temperate climate varies from 0 1 to 0 3 gm per cent. After continuous exposure to heat, especially where there is slight deficiency in intake, the salt content of sweat may fall

Salt deficiency in heat exposure usually results from excessive loss in the sweat, it may be aggravated by diarrhoea and vomiting When severe, it leads to secondary dehydration The loss of salt can be adjusted in heavy working conditions by an intake of 25 to 30 gm per day, half this amount suffices in the normal adult not sweating unduly

Salt loss is limited to some extent by reduction in the output in the urine In severe salt loss the electrolyte may disappear completely from the urine

Cardiovascular system Mention has already been made of the changes which occur in skin circulation on exposure to heat In addition there is a slight increase in blood volume following readjustment of water balance between the tissue cells and extracellular fluid

there is at first a small increase in cardiac output, which falls considerably when the posture is suddenly changed to standing, with a corresponding rise in pulse rate and fall of blood pressure. As the subject becomes acclimatized to heat these phenomena become less apparent These orthostatic variations in the circulation are useful to the physician as an indication of the state of cardiovascular acclimatization. For instance, in heat exhaustion the change in posture from lying to standing may provoke such violent circulatory changes that syncope results.

After exposure to very high temperatures or in an individual in whom the body temperature has risen very high, the compensatory changes in blood volume and circulation may be inadequate and shock may develop, accompanied by acute fall in effective blood volume and in blood pressures. Vascular collapse most commonly occurs in heat exhaustion It may be accompanied or succeeded by renal or hepatic failure

HEAT PYREXIA AND HYPERPYREXIA

DEFINITION

A rise of body temperature accompanied by general symptoms after exposure to intense heat When the temperature reaches or exceeds 107° F the condition is arbitrarily referred to as one of hyperpyrexia and a syndrome develops which may end fatally. The clinical picture originates from failure to control the body temperature consequent on inhibition of sweating; it may be complicated by coexistent electrolyte-water imbalance and by shock

AETIOLOGY

T[illegible]

endured by stokers, do not initiate the syndrome.

Hyperpyrexia appears most frequently in unacclimatized subjects or in individuals, for example miners, who have lost their acclimatization [illegible]

equally readily in the visitor to the tropics or the indigenous population

Certain predisposing factors are important. Anything that interferes with the evaporation or production of sweat may precipitate the syndrome. For instance, excessive clothing, lack of air movement, or enclosure in a confined space may prevent evaporation of sweat and

so limit heat loss Extreme dehydration may lower the production of sweat below the amount required to control heat loss by evaporation Acute febrile illnesses particularly malaria and pneumonia may also induce the onset by inhibition of sweating during the fever

Overproduction of heat is sometimes important Metabolism may be unduly excited by excessive protein intake, or by the overactivity of endocrine glands, especially the thyroid More commonly, excessive muscular exercise is responsible Pregnancy is also an important factor

A history of previous attacks of hyperpyrexia is unusual

PATHOGENESIS AND PATHOLOGY

[illegible]

after death depend largely upon whether the predominant clinical feature was the hyperpyrexia or vascular failure In either case, rigor mortis is rapid and the cadaver blood is fluid In cases which have been predominantly hyperpyrexial the brain is congested and the lesions therein are primarily neuronal, the pattern being degeneration and ultimately necrosis of nerve cells and replacement with glial tissue In rapidly fatal cases the neuronal degenerative changes predominate but in cases which have survived for some days there is considerable infiltration of the degenerate regions with glial cells Cases complicated by shock show congestion of the small vessels of the brain and minute haemorrhages into the brain substance In hyperpyrexial cases neuronal changes are most pronounced in the cerebellum, and to a smaller extent in the cerebral cortex, in shock the cerebellum is often unaffected and the lesion is mainly in the deeper layers of the cortex and the basal nuclei Pathological changes in organs other than the brain depend mainly on the existence or otherwise of vascular failure In cases which survive long enough and in which vascular failure has been prominent, centrilobular necrosis of the liver may occur and there may be renal changes similar to those of renal anoxia with damage to the tubular epithelium and medullary congestion associated with anaemic glomeruli In shocked cases petechial haemorrhages are common in most tissues including the mucous membrane of the upper small intestine, and the endocardium, peritoneum and pleura

CLINICAL PICTURE

The onset is abrupt and occasionally dramatic and totally unexpected (the so-called 'flash' hyperpyrexia) In a few cases there are well defined prodromal symptoms which appear and develop several days before the onset

Patients in whom the onset is rapid are frequently admitted in a state of delirium or coma, and on recovery may be unable to give a clear history. Where the onset is more gradual, however, there is usually a history of headache, drowsiness, restlessness, and mental confusion, often accompanied by progressive dizziness and sometimes an unsteady gait Anorexia, nausea and vomiting are common. There may be difficulty in speech and swallowing. Intense thirst is common, leading to heavy consumption of fluids with polyuria and frequency (estimated in a hot climate as two litres or more of urine and micturition more than four times in the day)

The patient may have observed a reduction of sweating during exercise, especially on the trunk.

By the time he is examined he is often in delirium or deep coma. If still conscious, he is restless, anxious and confused.

The oral temperature is very high. It may exceed 110° F The rectal temperature is about one degree higher

The skin is dry and flushed There may be some cyanosis of the extremities The dryness of the skin indicates the pathogenesis of the syndrome, i e. inhibition of sweating.

The pulse rate is fast; frequently over 130 beats per minute. There may be soft systolic cardiac murmurs and transient electro-cardiographic evidence of myocardial dysfunction The blood pressure is not grossly affected unless shock has appeared

The respiratory rate is high (30 or more respirations per minute). Breathing is shallow but not panting In the late states especially in coma it may be stertorous or intermittent. Breath sounds are prolonged but unless collapse is imminent and lung oedema has appeared there are no adventitious sounds Alkalotic tetany has been described.

Central nervous symptoms are pronounced and usually manifest from the onset. Mental changes and coma have already been mentioned In rapidly progressing cases, delirium or coma, when present at the onset, tend to persist to the end If the patient survives for some days before a fatal issue, early coma may temporarily regress and return terminally In the majority of treated cases, coma and delirium disappear quickly as the body temperature falls Incontinence of urine and faeces is common in comatose cases.

Convulsions, sometimes resembling Jacksonian epilepsy, and muscular twitchings, especially in the limbs, are common in the acute stages. The neurological physical signs are, however, irregular and vary from patient to patient and from time to time in the same patient They are most obvious in subjects in whom high fever is the predominant feature.

The presence of signs of salt deficiency in some cases has led to considerable confusion in the description of the syndrome. It should be

realized that in heat hyperpyrexia such phenomena are of secondary and not primary pathogenic significance

The urinary volume and constituents depend on the clinical state If salt deficiency already exists the volume is small and there may be little or no excretion of salt There may be some polyuria due to water diuresis initiated by drinking before the onset of hyperpyrexia In cases complicated by shock the syndrome of renal anoxia may develop (See pp 46, 49)

The blood shows no special features other than those associated with complications The blood urea nitrogen is usually a little raised, occasionally in patients with very high fever the total blood non-protein nitrogen may rise without a corresponding rise in urea nitrogen

Total blood and plasma chloride concentrations may be within normal limits, they are low if salt deficiency is present

Without treatment the severe case will die Death occurs either from the direct effects of the high body temperature or from shock.

The commonest complication is medical shock which may occur at any stage At first the effects of such vascular collapse are reversible but in a short time irreversible changes occur, particularly in the brain, liver and kidneys The onset of shock is shown by notable changes in the patient's appearance The temperature falls rapidly, often to below normal The skin becomes pale, cold, slightly cyanosed and often moist with sweat Respiration is rapid and shallow The blood pressures fall At first, the diastolic pressure drops more slowly than the systolic, so that the pulse pressure is reduced Ultimately the diastolic pressure may become unmeasurable The circulating blood volume is acutely reduced, with corresponding haemoconcentration indicated by rising erythrocytic count and haemoglobin concentration The conscious patient may become restless, irritable and anxious, coma or stupor may develop Watery diarrhoea is common and there may be incontinence

The urinary volume is reduced and the oliguria may pass into anuria with development of uraemia Sometimes evidence of liver dysfunction develops The liver becomes palpable and tender and there may be epigastric discomfort, nausea, bilious vomiting and diarrhoea and sometimes hiccup Mild jaundice sometimes develops and bile pigments may appear in the urine and faeces

The vomit and stools in this stage often contain fresh or altered blood Petechial haemorrhages may appear in the skin and mucous membranes Signs of pulmonary oedema may develop terminally

PROGNOSIS

With prompt treatment the mortality is low Death occurs in 24 hours in most fatal cases, some may survive for as long as 12 days Early death results largely from the high fever, later deaths from shock The

prognosis in an individual subject is determined by the length of illness, the height and duration of the fever, and the presence or absence of shock Shocked cases or those with very acute onset and rapidly developing coma have the poorest prognosis.

With adequate treatment the recovery should be rapid (i e. a matter of few days) and permanent In some patients, however, unpleasant sequelae may develop, including changes in personality, persistent and irritating amnesia, severe headaches and various nervous tics

DIAGNOSIS

Breakdown of the heat controlling mechanism does not occur except after prolonged exposure There is often a history of predisposing causes Clinical diagnosis can be made from the high fever, the flushed dry skin, and the neurological signs, provided other causes of fever can be excluded, *especially falciparum malaria in which hyperpyrexia may occur as a complication The blood must always be examined for malaria parasites*

TREATMENT

Treatment is designed to lower the temperature and promote sweating For the immediate reduction of the temperature any available method of cooling should be used

The patient should be kept quiet and nursed in a cool or air-conditioned room The body temperature can easily be reduced by evaporation of water from the skin surface The patient is stripped, covered lightly with a wet sheet, and fanned vigorously, so as to keep up continuous evaporation Continual spraying with cold water or immersion in a cold bath will be equally effective During the operation the temperature must be recorded every few minutes It usually falls rapidly after the start of treatment. When it has fallen to about 102° F, active treatment should be stopped, otherwise the patient may collapse. The temperature usually continues to fall to normal or below without further treatment Secondary rises of temperature may occur within the next few hours or even days. These may require treatment on the same lines In most cases natural sweating is restored after the first treatment In more severe cases the re-establishment of sweating is slower and treatment may have to be repeated

Complications are treated as they appear. Shock and dehydration need parenteral fluid therapy (see pp 61, 127) Intravenous infusion is not otherwise indicated

Sequelae are often resistant to treatment These include personality changes and neurological signs, such as involvement of the cranial nerves or hemiplegia, which tend to persist. Persistent headache is

common but usually clears up after weeks or months, it may be relieved in some patients by nicotinic amide

HEAT EXHAUSTION

I SALT/WATER DEFICIENCY

This condition is most frequently seen in hot conditions, especially in association with heavy manual labour Sweating is not inhibited and heat loss is *thus not affected The body temperature is seldom elevated* much above normal Disturbances of body salt water balance and of the cardiovascular system are always present The most severe cases are dehydrated and shocked

AETIOLOGY

Heat exhaustion *occurs commonly during the hottest time of the year* It appears in visitors and local inhabitants of all ages and in either sex The most important predisposing factor is heavy and prolonged sweating, with failure to replace water and salt

Coexistent febrile illnesses, especially malaria, are also important as are gastrointestinal disturbances involving diarrhoea and vomiting

CLINICAL PICTURE

There is usually a prodromal period lasting several days during which

develop early Sweating is free in all parts of the body The urinary output is commonly low

Visual and aural disturbances, such as 'spots in front of the eyes' and 'ringing' in the ears may occur In miners and other manual workers a frequent history is 'I felt giddy, and took a big drink of water, after which I promptly vomited and felt cramps in my limbs'

The seriously affected *patient always vomits Muscular cramps are* more common in patients who are vomiting It is often difficult to determine from the history whether there is obvious water or salt deficiency, but consideration of the tremendous losses of fluid and salt *during* heavy work will usually indicate the possibility of direct deficiency

On examination the patient is extremely exhausted In serious cases he may be restless and anxious or lightly comatose Central nervous system signs are, however, much less prominent than in heat

hyperpyrexia They are usually of short duration and respond readily to treatment

The oral temperature may be normal or subnormal, or slightly raised.

The skin is cold, moist, pale and inelastic. The facies are pinched, the eyes sunken, the malar bones prominent Sweating may be profuse.

In comatose cases the respiration may be deep and stertorous. Where vascular failure has developed there may be evidence of pulmonary oedema

Most patients vomit frequently. The vomiting is not always accompanied by nausea and may be intractable. It is often followed by muscular cramps, which may be fleeting or severe and occur most commonly in the legs, arms and abdominal muscles. Occasionally there may be tetanic carpopedal spasm

The pulse rate is nearly always very fast, very occasionally there may be noticeable bradycardia.

In mild cases the systolic pressure may fall to below 90 mm Hg but the pulse pressure is low, since the diastolic pressure tends to remain [illegible]

In severe cases vascular failure appears The pulse rate rises, sometimes to 150 to 200 beats per minute. Both systolic and diastolic blood pressures fall. The pulse may be imperceptible at the wrist. The circulating blood volume is grossly reduced; the viscosity of the blood increases and the haemoglobin concentration and the red cell count temporarily rise.

Urine The urinary volume is reduced to 500 ml or less per day When shock has appeared, there may be complete suppression of urine, which may be temporary or permanent, leading to the renal anoxia syndrome The urine may contain albumin and hyaline and granular tubular casts. It is unconcentrated; chloride is present in low concentration or absent

Blood The whole blood and plasma chloride and sodium concentrations are low, especially if vomiting is or has been severe The blood urea nitrogen concentration is high, of the order of 100 mgm per cent, even in cases without obvious renal dysfunction In acute uraemia accompanying the suppression of urine the concentration may be very high.

PROGNOSIS

Uncomplicated and correctly treated cases recover very rapidly. Shock considerably worsens the prognosis, although it usually responds to treatment. The outlook is bad in anuric cases

Relapses are uncommon if the salt/water balance is maintained and acclimatization re-established There is no indication for removal of the patient from the hot environment

DIAGNOSIS

This history of exposure to heat, especially under working conditions, and the circumstances of the onset are usually diagnostic In severely affected patients other causes of vascular collapse must be excluded *In all cases the blood must be examined to exclude malaria, especially falciparum* The presence of malarial or other infection does not affect the treatment required for adjustment of the electrolyte balance and plasma volume There is often no detectable chloride in the urine, in any case the chloride content is extremely low Reduction of chloride and sodium levels in the blood will place the diagnosis beyond reasonable doubt

Chloride in the urine may conveniently be determined by the Fantus test, as follows To 10 drops of urine in a test-tube add 1 drop 20 per cent potassium chromate Then add 2 9 per cent silver nitrate drop by drop, shaking with each drop The end-point is the appearance of a yellow-red colour. The number of drops of the silver salt solution roughly equals the chloride in gms per 24 hours

TREATMENT

The aim of treatment is to restore the electrolyte/water balance and the blood volume where necessary

The patient should be treated in bed An input output fluid balance account should be kept The volume of each specimen of urine passed should be recorded Most cases can be treated orally

Mild cases are given orally up to 5 or 6 litres of fluid, and a total of 25 to 40 gm salt (including the salt in the diet) in the first 24 hours It can be administered in capsules or in foods such as soup Water must be given as well as salt

In severely dehydrated and shocked cases or in those with intractable vomiting fluid must be given parenterally

An initial pint of plasma given in half an hour is required in shocked patients

If dehydration is severe, the first pint of isotonic saline should be administered in about a quarter to half an hour, and followed by a further pint in half an hour Infusion thereafter should be slower, i e at the rate of 1 pint every 4 hours by drip Not more than 6 to 9 pints should be given in the first 24 hours It is seldom necessary to continue parenteral treatment longer than this

A check should be kept on the urinary chloride concentration during

parenteral treatment. 'Hypotonic' saline (1 part isotonic saline plus 2 parts isotonic glucose) should be substituted for isotonic when the chloride concentration begins to rise

Response to treatment is usually rapid, even in the severely dehydrated individual The mildly affected patient may be fit to return to work in a few days.

II PRIMARY WATER DEFICIENCY

During the working period of the day, the water intake of the average individual in hot climates fails to keep pace with losses in sweat and insensible perspiration The deficit which results, so-called 'voluntary dehydration' is usually made good in evening and leisure hours, if fluid is available In these circumstances, primary water deficiency of clinical significance rarely occurs Thirst, however, is an inconstant and often inadequate signal of water deficiency, and fluid intake may be influenced strongly by habit.

Headache, giddiness, fatigue, oliguria and slight elevation of the body temperature are features of mild water deficiency arising when water intake is inadequate for unaccustomed and high levels of activity and sweating More severe features, attendant upon haemoconcentration and vascular collapse, occur generally only in abnormal circumstances, for example, in men stranded without water in a desert.

Primary water-deficiency is diagnosed readily by the clinical signs common to all forms of dehydration. It is differentiated from salt-deficiency (in which dehydration is secondary) by the absence of muscle cramps, by detectable amounts of salt in the urine, and by normal or apparently increased plasma electrolytes In mild cases, confusion may arise between water-deficiency and minor heat syndromes such as *heat syncope* or *exercise-induced heat collapse* The latter are merely expressions of inadequate acclimatization to heat, and disappear rapidly when sufferers are allowed to rest in cool surroundings

III ANHIDROTIC HEAT EXHAUSTION

DEFINITION

Thermogenic anhidrosis, tropical anhidrotic asthenia This syndrome was first described in World War II There is some inhibition of sweating, principally on the trunk and limbs, but not on the face and

disturbances These are, however, not essential features

PATHOLOGY

It is not known whether the inhibition of sweating is central or peripheral The high sweat chloride is regarded by some as an indication of exhaustion of the sweat glands Others hold that pathological changes found in the glands account for the inhibition of sweating In any given area of skin, however, relatively few glands are obviously affected In those affected there is some hyperkeratosis which appears to obstruct the ducts, leading in some to rupture into the surrounding epithelium which becomes disorganized, producing an intradermal vesicle filled with clear fluid The local lymphatics are dilated and the associated blood vessels congested

CLINICAL PICTURE

Thermogenic anhidrosis usually develops after long exposure to high temperatures. The onset is usually gradual The symptoms are most severe during the hottest part of the day

History The patient complains of exhaustion, dyspnoea and cardiac palpitation after work or exercise Most patients suffer from anorexia and epigastric discomfort, giddiness, frontal headache and insomnia There are frequently subjective feelings of warmth and tightness in the affected skin The symptoms pass off with rest in cool conditions, but as the syndrome progresses, increasing periods of rest are needed, until finally work becomes impossible

The patient usually gives a history of extensive prickly heat, which may have improved considerably some weeks before the syndrome develops He also often notices that sweating on the body but not on the face progressively diminishes as the syndrome develops Sometimes this may be preceded by a short period of excessive sweating

The patient is restless and apprehensive The oral temperature lies between 99° and 102° F The pulse rate is fast Respiration is deep and fast, the rate may exceed 40 per minute In the uncomplicated case the blood pressure is unchanged

On the limbs and most of the trunk the skin is dry There may be small isolated islands of sweating Sweating is free on the face and neck, the palms, soles, axillae and groin are usually moist The distribution of sweating is thus similar to that in so-called 'cold sweating'

The skin eruption or mammillaria is characteristic It is composed of myriads of tiny greyish papules about 1 mm in diameter, commonly surmounted by vesicles containing clear fluid These lesions occur in patches distributed on the trunk and on the upper dorsal aspect of the arms and legs Superficially the condition resembles goose flesh but the skin hairs are not involved It may be mistaken for prickly heat, but there is no erythematous ringing of the papules and there is no itching

or prickling. Between the papules and on the rest of the trunk and limbs the skin is dry and warm. The lesions commonly develop first on the arms, and may spread to the trunk and finally the legs. In some cases the arms, legs and trunk are involved simultaneously. The papules do not appear on moist areas and are found on the head and neck only very exceptionally.

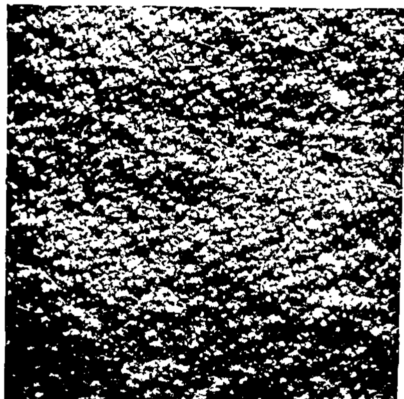


FIG 17 Mammillaria in case of thermogenic anhidrosis
[Courtesy of Transactions of Royal Society of Tropical Medicine and Hygiene, and Dr R H Mole]

Mammillaria may occur without anhidrosis or symptoms of exhaustion. In such cases, sweating over the affected area is, however, often notably reduced, and there is usually a history of previous severe prickly heat which cleared before the appearance of mammillaria.

Firm oedema of the fingers and arms may occur in some cases and be associated with enlarged discrete axillary or inguinal lymph glands.

Changes in the blood or urine depend on the state of the body water/salt balance.

Polyuria due to water diuresis with dilute urine but with a normal output of salt may occur in cases in which thirst is a prominent feature

The salt concentration of the sweat is high and frequently exceeds 0 5 per cent

Prognosis The uncomplicated condition is not fatal Recovery occurs with treatment.

TREATMENT

The only treatment required is rest in cool surroundings Where there are disturbances of water/chloride balance, these should be controlled by adequate administration of water and salt, parenteral administration is seldom necessary

There is a rapid response of temperature, respiration and pulse The skin changes disappear more slowly, and are commonly succeeded by branny desquamation, particularly on the limbs Enlarged lymph glands and oedema subside slowly Within a few days there is increasing ability to exercise without return of symptoms Sweating returns first as a rule on the trunk At the beginning of treatment, exertion, exposure to heat, or injection of pilocarpine cause a return of symptoms and the peculiar distribution of sweating Later exposure produces no symptoms and a normal sweating reaction

Full recovery may be expected in about a fortnight Relapses are common, especially if treatment is too short It is advisable to remove the patient from the hot environment if possible

PRICKLY HEAT

DEFINITION

Miliaria rubra An extremely common and irritating superficial skin eruption distributed widely over the tropics and subtropics

AETIOLOGY

The cause is uncertain Secondary infection with pyogenic organisms and sometimes fungi occurs and affects the progress of the condition, but such infection is not regarded as the primary cause Pathological changes in the sweat glands suggest that the ducts may become mechanically blocked by soggy swollen epithelium

Prickly heat is especially common in hot humid regions where sweating is likely to be heavy and continuous Infants and children with thin skin and obese individuals with multiple skin folds are often

severely affected Recent arrivals usually suffer most Males are affected more commonly than females

CLINICAL PICTURE

The lesions develop soon after arrival in the hot humid area. They begin as numerous scattered small papules a millimetre or two in diameter, which soon develop vesicles, containing clear or slightly milky fluid Each papule may be surrounded by a halo of erythema, or there may be a general erythematous background upon which the papules develop In some cases the first sign is a patchy erythema which appears on heating and goes on cooling Papules soon appear in large numbers in such areas and develop vesicles.

The lesions are very irritating and the itching and prickling leads to involuntary scratching, followed invariably by secondary infection In some parts of the body a purulent eczematous lesion may result in this way, in others the papules subside and are replaced by a white powdery desquamation In chronic cases the affected skin is thickened and erythematous and batches of papules appear and subside at intervals Itching may persist throughout the condition.

Prickly heat tends to appear in parts of the body where there is close contact with clothes, for example, around the waist or on the shoulders. It is common in friction areas, for example, on the wrists where the coat or shirt cuff moves over the skin, or in areas where skin is in contact with skin, for instance in skin folds in obese individuals or below the breasts Its relation to the local production of sweat is not clearly defined Most of the areas mentioned tend to be moist, but the lesions also commonly occur on the backs of the hands where sweating is minimal

In infants practically the whole skin may be involved, and secondary infection may lead to serious results. It may be necessary to remove the child from the district to some cooler spot

Prickly heat is at its worst in the hot wet season and may clear completely in the cool It tends to recur in a given individual with the advent of the hot season, usually with diminishing severity as the sufferer becomes more used to dealing with it

In some individuals the general effect is intolerable and psychological reactions are not uncommon. Sleep may be difficult Unless caused by secondary infection, general reactions such as fever are negligible.

DIAGNOSIS

Prickly heat can be diagnosed by its appearance and distribution. The groups of small papules, with or without crowning vesicles, sur-

rounded by haloes or background of erythme, are usually unmistakable In the early stages they may be mistaken for the mammillaria of thermogenic anhidrosis (see p 130) but the latter can be distinguished by the absence of local sweating

TREATMENT

The lesions may be very difficult to deal with in a delicate skin and sometimes the only way out is the removal of the individual to a cooler climate Recovery in a temperate climate is usually very rapid and complete so long as secondary infection is not severe

The part should be washed gently with an antiseptic soap It may be necessary to determine by trial and error which of the latter is suitable, since some may irritate the lesions and cause exacerbations The soap may be allowed to dry for 20 minutes or so on the lesions It is then washed o[illegible]

Local [illegible] from patient to patient What is [illegible] nes harmful to another [illegible]

from time to time during the day

Pyogenic infections must be treated before the above treatment is applied Local permanganate baths given for half an hour twice daily and followed by zinc oxide dusting powder may be effective

PREVENTION

Local treatment is unsatisfactory without concurrent preventive measures The subject should avoid high temperatures as much as possible He should forgo unnecessary exertion or frequent drinking, especially tea, which may enhance sweating Tepid baths should be taken twice a day, and hot baths avoided unless there is ample time for [illegible]

Care must be taken to see that the skin is thoroughly dried after bathing The frequent use of ordinary alkaline soaps may be harmful Frequent drying of the skin with handkerchiefs or towels will help keep the lesions under control

Controlled sunbathing is beneficial especially for children, sea bathing often exacerbates the condition

TROPICAL FATIGUE

Neurotic reactions falling under this heading are advantageously divided into acute and chronic. The existence of such syndromes cannot be denied, but their relationship to the thermal element of the environment is less clear. In the tropics, they affect mainly the white immigrants, on whom the sociological and psychological stresses of a small community in untraditional surroundings have an effect which should not be underestimated. Highly motivated individuals are rarely implicated.

Acute neurotic reactions: there is no doubt that human performance of skilled tasks, involving mental concentration, accurate muscular co-ordination, and speedy reaction-times deteriorates as ambient temperatures rise. After several weeks or even days of working under such difficulties, some individuals become irritable, disinclined to continue, and even hysterical. They recover only when removed from their environment, to which they are temperamentally unsuited.

Chronic neurotic reactions: tropical deterioration: numerous minor dissatisfactions inevitable to small communities combine with physical stresses imposed by late hours, alcohol [illegible]

[illegible]

and actual physical health. It is not enough to judge such people as unsuited for life in the tropics, and the ecological problems involved deserve further study and research.

EFFECTS OF EXPOSURE TO LIGHT
SUNBURN

DEFINITION AND AETIOLOGY

Acute solar dermatitis. Sunburn is an acute dermal reaction to exposure to ultraviolet light of wavelength 2900 to 3200 A°. Heat plays no direct part in its appearance, although heating may sometimes make the skin more sensitive to ultraviolet light. Reactions identical to sunburn occur after exposure to sources of ultraviolet light or to 'cold' light such as that reflected from snow or water.

The essential aetiological factor is exposure to direct sunlight for sufficient time.

The severity of the reaction depends on many factors especially the duration and intensity of exposure, and the area of skin exposed. Certain areas, including the skin of the back of the trunk and neck and the popliteal regions, are highly susceptible. Skin pigment protects against

ultraviolet light dark or coloured skin burns much less readily than fair Slow acclimatization to exposure leads to protection from increasing thickness of the horny layers of the epithelium and deepening pigmentation

CLINICAL PICTURE

Sunburn follows exposure after a symptom-free period of a few minutes to some hours

The first indication is erythema of the exposed parts accompanied by itching In mild cases the erythema may be transient, fading in a few hours, followed by complete recovery In more severe cases the erythema increases and the affected skin becomes oedematous and slightly raised The edges often follow the pattern of the exposure, and there is frequently a surrounding well developed arteriolar flare Vesicles and bullae containing clear fluid rapidly form on the surface

The burned area is intensely painful and sensitive There may be intolerable pruritus, especially in the healing stages

Unless there is secondary infection the inflammatory reaction fades in the course of a few hours or days, depending on its severity Blisters either rupture or absorb, and are followed by desquamation and peeling

The area involved may show irregular hyper- and hypo-pigmentation after subsidence of the acute lesion Areas which were covered by blisters are usually depigmented

[illegible]

causing considerable local damage and scarring

Areas of skin which have been sunburned are often left with increased sensitivity to ultraviolet light and may burn more easily on re-exposure to sunlight

Most cases show some general symptoms including headache, malaise and mild nausea In severely burned patients there may be high continuous fever, and considerable prostration with fast pulse and respiration Nausea and vomiting are common and often severe Vascular failure, sometimes fatal, may appear in individuals in whom large areas of skin are involved

The general reaction in mild cases lasts only a few hours In more severe cases its duration depends on the extent of burning and the development or otherwise of secondary sepsis

PROGNOSIS

There is a tendency to regard sunburn lightly but it must be realized that the general reaction may be very severe and sometimes even fatal

The progress of local lesions depends on the degree of exposure and the development or otherwise of secondary infection. Usually recovery is complete.

TREATMENT

The burned area should be carefully cleaned with calamine lotion or liquid paraffin. Analgesic or antiseptic ointments and soap are to be avoided. Blisters should be ruptured and the peeling skin removed. Exposed areas should be painted with calamine lotion containing 0.5 per cent crystal violet. Badly involved areas may be temporarily covered with calamine compresses. After the subsidence of the early inflammatory reaction, further application of calamine or zinc oxide plus castor oil ointment is advisable.

Great care should be taken to avoid secondary infection of blistered areas, which may be bathed at intervals with antiseptic solutions such as weak mercuric chloride (1 4000). Local sepsis is treated on general lines

[illegible]

stage

The sunburn should be treated like a burn from any other cause and protected against injury if necessary by cradling.

General treatment aims at sedation, the control of secondary infection, and avoidance of further exposure.

Severely burned patients may be given barbiturates or morphia if they are restless or sleepless. The administration of penicillin or other antibiotics, or of sulphonamides may be necessary in severe secondary infection.

Shock and dehydration must be treated on general lines. (See pp 61, 127.)

PREVENTION OF SUNBURN

Sunburn can be avoided by limiting direct exposure by the use of sensible clothing, sun umbrellas, etc. Window glass affords considerable protection since it absorbs most of the active wavelengths. Acclimatization may be achieved, especially in brunettes, by graded exposure.

Protection is also provided by the use of chemical screens applied to the skin in the form of powders or creams.

Cosmetic face powders and creams have some protective properties but these can be enhanced by the addition of certain chemicals, for example, tannic acid (5 per cent), quinine (5 per cent), p-aminobenzoic

acid and salol (10 per cent), which selectively absorb the active ultra-violet light

Creams containing these agents should be applied every 3 or 4 hours [illegible]

for promoting pigmentation on exposure without undue risk of burning

The use of creams and lotions containing light-filtering agents may sometimes interfere with sweating and the escape of body heat Dermal sensitivity to the contents may exist, leading to various unpleasant skin eruptions

XIII

LEISHMANIASES

INTRODUCTION

THESE are diseases due to infection with one or other of a number of species, and probably strains, of protozoa belonging to the genus *Leishmania* Man appears to be the sole mammalian host of some species in some areas; in others there are additional mammalian hosts, and in yet others man is only a casual host, the essential hosts being animals All the parasites, in nature, are conveyed by sandflies belonging to the genus *Phlebotomus*, in these they undergo a multiplicative cycle of development Each species of *Leishmania* is conveyed only by certain sandflies, for example *L. donovani* is transmitted by species of *Phlebotomus* which will not convey *L. tropica*.

It is convenient to classify the leishmanial diseases of man primarily on a clinical basis into three types. These are visceral, cutaneous, and muco-cutaneous leishmaniasis The visceral disease of the Old World is a reasonably clear-cut entity and conveniently can be ascribed to *L. donovani* The cutaneous disease, of which there are several clinical forms, in the Old World can equally be ascribed to *L. tropica* The muco-cutaneous form, the classical espundia of South America, can be attributed to *L. braziliensis* In this classical form the infection begins cutaneously and later spreads to the external mucosae embolically, but it does not invariably do so, and in some parts of South America the lesions closely resemble certain of those due to *L. tropica* infection in the Old World Furthermore, in the Old World where *L. tropica* is held to be the causative parasite cases of espundia occasionally are reported Again, what clinically is visceral leishmaniasis, or kala-azar, occurs to a minor degree in South America.

The organisms recovered from the various types of human infection show differences in culture media, in experimental animals, and especially on serological testing and in their response to drugs, such differences also are evident between organisms recovered from different areas of endemicity of apparently the same species.

VISCERAL LEISHMANIASIS

DEFINITION

Visceral leishmaniasis, or kala-azar, is a condition due to infection of reticulo-endothelial cells throughout the body with the protozoan parasite *Leishmania donovani* The infection is conveyed from man to man by the bites of certain sandflies (*Phlebotomus* spp) in which the parasites undergo a multiplicative cycle The resultant disease is characterized by a lengthy incubation period, an insidious onset, and a chronic course attended by irregular fever, increasing enlargement of the spleen and of the liver, absolute leucopenia with marked neutropenia, anaemia and progressive wasting The mortality is high, death in fatal cases usually occurring within a couple of years

GEOGRAPHICAL DISTRIBUTION

Kala-azar is prevalent in various parts of India, especially in the Bengal area and adjacent Assam, in parts of China and Manchuria, throughout the Mediterranean basin, and in tracts of Abyssinia, the Sudan, and north Kenya It also occurs in certain regions of West Africa, and it is found widely though sparsely in South America Hot and moist climatic conditions, such as those obtaining along great rivers, favour the vector species of sandflies and the propagation of the disease, in such circumstances, for example along the Brahmaputra valley in Assam, kala-azar periodically assumes devastating epidemic proportions

AETIOLOGY

Though primarily a parasite of man natural *Leishmania donovani* infections occur in some other animals, especially dogs, many of the latter are found to harbour the parasites in the Mediterranean and the Chinese areas of incidence of the disease The correlation between human and canine leishmaniasis is not constant, in those parts of India where the human disease is common dogs are rarely found to be infected, in Morocco and in Persia, where canine infection is common, the human disease is a rarity.

The parasite in man lives in the form of morphologically characteristic, inert, oval bodies (Leishman-Donovan bodies) in reticulo-endothelial cells throughout the body The Leishman-Donovan bodies multiply by simple fission, are liberated by rupture of their containing cells, and are taken up by further similar cells in which they again multiply They appear in small numbers of macrophages in the blood; in this vehicle they are distributed to all parts of the body.

The most important vector sandflies are *Phlebotomus argentipes*, *P. major* and *P. major* var *chinensis*, and *P. perniciosus*, other proven vectors include *P. sergenti* var *mongolicus*, *P. langeroni*, *P. intermedius* and *P. longicuspis*. In some regions of endemicity the vector species of sandflies have not been determined. Only female sandflies are blood feeders. On ingesting *L. donovani* in blood these are liberated on digestion of the meal in the midgut of the insect The Leishman-Donovan bodies there rapidly become flagellate leptomonads which migrate forwards to the cardia, and then to the pharynx and to the buccal cavity of the fly. They multiply rapidly and vigorously by simple division and, under suitable conditions, a massive growth of leptomonads blocks the oesophagus and pharynx On the fly's attempting to take another blood meal some of these flagellates escape from the proboscis into the bite wound, and so the infection is transmitted to a fresh host. The injected flagellates in this host rapidly assume the Leishman-Donovan form, are taken up by macrophage cells, and eventually are disseminated as already described.

There are certain peculiarities in the clinical features of kala-azar as encountered in the various areas of its distribution For example, the Mediterranean disease affects more particularly infants, and is associated with a high incidence of the infection in canines; in India, on the other hand, kala-azar occurs in persons of greater age, though its peak incidence is in children of about 12 years, and canine infection is almost unknown The Sudanese and the Chinese forms each have clinical peculiarities Such differences have in the past led to the introduction of a number of specific names for the causative parasites; there is no justification for many of these

Though *Leishmania donovani* is the name now generally accepted for the organism causing kala-azar in the East, it is not uncommon to find *L. infantum* or *L. donovani* var *infantum* used in reference to that causing kala-azar in the Mediterranean There are no morphological, cultural or antigenic distinctions between the two, and the latter name is warranted solely for descriptive convenience

PATHOLOGY

Leishmania donovani parasitizes reticulo-endothelial cells in any part [illegible]

spleen enlarge, and the red bone marrow extends beyond its normal limits. Reticulo-endothelial tissue in the lymphatic glands, in the lungs, in the intestinal wall, and in the skin, sometimes is heavily parasitized, the degree to which these are affected varies with the strain

of parasite and from one case to another There are almost no tissues from which Leishman-Donovan bodies have not at some time been recovered on post-mortem of cases of kala-azar and, for this reason, almost every secretion or discharge from the body at some has been reported to yield parasites



FIG 18 Kala-azar Leishman-Donovan bodies in spleen puncture material [From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

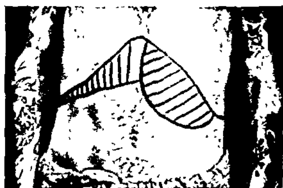
Histologically the outstanding feature of parasitized tissue is the enormous proliferation of cells of the macrophage type, their presence overshadows the normal structure of the organ, and many of the macrophages in the tissue will be seen to contain Leishman-Donovan bodies An affected organ, for example the spleen, becomes much engorged and expands until it may largely fill the abdomen, there is little fibrous tissue formation, and so there is no tendency to hardening such as is seen in the 'ague cake' spleen of a chronic malaria infection In the liver the Kupffer cells, which usually are heavily parasitized, proliferate freely Fibrous tissue formation in the liver which occurs terminally may produce an interlobular cirrhosis, this probably is caused by nutritional changes and not directly by the parasitization That fibrous tissue formation is not a feature of the histological picture in kala-azar not uncommonly is further shown by the return to normal size of an enormously enlarged spleen and liver, and their restoration to normal histological structure after effective treatment

Certain changes occur in the peripheral blood in kala-azar There is an absolute leucopenia to below 4000 per cu mm, due to marked diminution in the number of the granular leucocytes, with an associated mononucleosis The neutropenia in the later stages of the disease may become a total agranulocytosis, and this development commonly is followed by the fatal complication, cancrum oris There is a slowly progressive anaemia, the red cells falling in number to between 2 and 3 million per cu mm, the red cells tend to be hyperchromic and macrocytic, but nucleated cells are unusual Red cell fragility is increased, the sedimentation rate is always high, and the platelet count is reduced, usually to 200,000 per cu mm The indirect van den Bergh reaction usually is positive The total plasma protein is low and there is an inversion of the albumin-globulin ratio, the serum albumin being much reduced and the gamma globulin increased This reversal in the balance of serum protein, probably due to liver dysfunction, provides the basis for the formol-gel, the antimony and other serum tests employed in the

clinical diagnosis of kala-azar The blood and plasma changes may be contributed to in old standing cases by hypersplenism.

CLINICAL PICTURE

The time elapsing between an infecting sandfly bite and the development of clinically demonstrable kala-azar varies greatly Incubation periods of as short as two weeks and of as long as eighteen months have been recorded. In view of its usually insidious development, and the characteristic absence of prostration even during periods of high fever



in this disease, many patients present themselves for diagnosis weeks or months after its onset They then do so because of abdominal swelling caused by enlargement of the spleen and the liver. In cases of this type the patient usually seeks advice between three and six months after infection, but sometimes the period may lie between one and two years. Though the onset commonly is insidious, in some cases it is acute and simulates the start of an attack of enteric or of malaria; the patient then seeks advice much earlier

In its early stages kala-azar is not easy to diagnose on clinical grounds when its presence is unsuspected. There is indefinite ill-health and lassitude, but there are no constant physical signs. There are irregular fever, a low blood pressure, and a high pulse rate; the changes in the blood picture soon become evident and these, particularly the leucopenia, should suggest the diagnosis.

increase in size has been likened to that of a pregnant uterus, ultimately it may largely fill the abdomen and extend into the pelvis The liver enlarges to a lesser degree, but commonly it reaches more than half way to the umbilicus From time to time patients may be encountered in whom the spleen enlarges but the liver does not do so, the reverse may be encountered, where gross enlargement of the liver is unassociated with appreciable enlargement of the spleen The enlarged spleen and the enlarged liver are neither painful nor tender on pressure

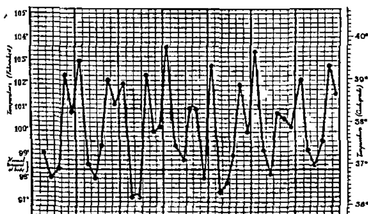


FIG 20 Temperature chart in kala-azar, showing intermittent or remittent fever with double diurnal rise
[From E. Noble Chamberlain, *A Textbook of Medicine* John Wright & Sons Ltd Bristol, 1951]

Sometimes there is jaundice, especially late in the disease, it is held to be of bad prognostic significance In cases of kala-azar from China and the Sudan general enlargement of the lymphatic glands has been reported, but this is not a feature of the disease elsewhere Though the appetite usually is good, and indeed may be voracious, there is steady bodily wasting, in time the patient becomes emaciated, with a protruberant abdomen due to the gross swelling of the spleen and of the liver

The fever, which is intermittent, remittent, or continuous, recurs irregularly, a peculiar character of it is that the patient is rarely prostrated, as he does not suffer from the usual subjective symptoms of fever Delirium, even in the last stages of the disease, is most unusual The temperature at some time during the course of a febrile attack will show a double, or a treble, diurnal rise to high peaks These febrile attacks last from some days to a few weeks, they are followed by periods of apyrexia also of irregular duration Sometimes no periods of fever are observed

The skin is dry and rough; in dark-skinned races the natural pigmentation of the skin over the malar bones and temples, and around the mouth, is deepened; it is from this that the disease derives its name (Black Sickness). The hair becomes dry and brittle, and tends to fall out, even children may become almost bald, but the hair grows again after specific treatment of the infection.

Oedema of the extremities is not uncommon, particularly in the under-nourished and debilitated, ascites due to cirrhosis of the liver which, as already stated, is probably a manifestation of nutritional disorder, may be seen terminally.

Other tissues and organs which particularly are involved by the parasitic infection in some cases include the lungs and the intestine. The lungs are invariably involved to some degree, an irritant cough is usual, though physical signs of a pulmonary lesion adequate to account for it are absent. Broncho-pneumonia and similar complications, due to superadded infections, are common; these are probably attributable to a diminished resistance to infection due to the leucopenia. Diarrhoea and even dysentery are also common, it is improbable that these are predominantly due to a massive invasion of the tissues of the bowel wall by parasites, they, also, are probably a result of increased susceptibility to superadded infections.

There is considerable evidence, particularly in India, that comparatively mild and self-terminating cases of kala-azar occur; the mortality from the untreated disease even there is at least 75 per cent; death usually follows within two years of the onset.

POST-KALA-AZAR DERMAL LEISHMANIASIS

An important and not uncommon sequel of visceral leishmaniasis in India, and less frequently in China and the Sudan, is the development of a peculiar dermal localization of the parasite. A year or so after an attack of kala-azar has apparently been cured by specific treatment lesions of the skin which contain *Leishmania donovani* make their appearance. Their development is not associated with marked ill-health. These dermal lesions vary considerably in appearance; some are erythematous, on the face commonly these assume a butterfly distribu-

resemble leprosy nodules, they may be very numerous; they rarely ulcerate, and large numbers of *L. donovani* can be recovered from them. A diagnosis of post-kala-azar dermal leishmaniasis is made on the time

of its appearance after recovery from kala-azar, and the recovery of *Leishmania donovani* from the skin lesions

DIAGNOSIS

As in every other parasitic infection, the diagnosis of visceral leishmaniasis fundamentally rests on the recovery and recognition of the causative parasite The parasites almost invariably can be recovered with relative ease from the spleen from the bone marrow, from the liver, or from the blood While the numbers present in any of the tissues, especially the blood, may be so small that direct examination does not reveal them, culture[1] will usually do so

Needling and aspiration of material from an enlarged spleen, the sternal or some other red marrow cavity, or the liver afford the best means of finding parasites in ordinary stained smears Commonly, but not invariably, Leishman-Donovan bodies are present in great numbers in any of these sites when the disease is well advanced They are recognized by their characteristic morphology and intracellular location, apparently isolated and free parasites are the result of rupture of the large endothelial cells while making the smear

In addition to a direct examination of stained smears the patient should always be given the benefit of a culture of material aspirated from such sites In the case of the blood, parasites perhaps may with difficulty be found after prolonged search of specially prepared stained films, nevertheless, culture, preferably repeated, of single drops of venous blood taken during a febrile period will always give a growth of flagellates, blood must not be sown in excess on the medium, which must be entirely free from any secondary bacterial contamination or no growth of flagellates will be obtained

The characteristic changes in the blood give an early indication of the development of visceral leishmaniasis Outstanding is a gross leucopenia, due to a neutropenia, which is associated with a relative mononucleosis, there is a progressive fall in the red cell count to 3 million per cu mm or less

Various serum tests are helpful in diagnosis, though they are not peculiar to this condition The formol-gel (aldehyde) test is performed by adding one drop of commercial formalin to about 1 cc of the patient's serum in a tube, the mixture is left to stand at room temperature A strongly positive formol-gel reaction is indicated by opacity of

[1] Leishman-Donovan bod [illegible]

[illegible]

before being discarded Bacterial contamination rapidly kills the protozoa

the serum, which also becomes solid and so resembles boiled white of egg, within two hours of performing the test There are diminishing degrees of positivity down to a weakly positive formol-gel reaction, which is read when opacity but no solidification is evident within twenty-four hours of setting up the test It is opacity which is the *characteristic of a positive formol-gel test; solidification is not of importance* in its interpretation The formol-gel test becomes positive within a month or two of the development of the disease, and it returns to negative after successful treatment and restoration to normal of the plasma proteins.

The antimony (Chopra's) test is performed by mixing a 4 per cent solution of urea stibamine with a ten times dilution of the patient's serum in distilled water. An immediate heavy flocculum, which settles on standing within half an hour, indicates a strongly positive reaction; a fine flocculum shows a weaker positive reaction; with a negative reaction there is no precipitate. This test may be positive in cases where the spleen is much enlarged due to causes other than leishmaniasis.

The ordinary laboratory animals are insusceptible to infection with *Leishmania donovani*, but the hamster (*Cricetulus* sp) is very susceptible to it and this animal is much used in experimental work on the parasite

TREATMENT

The trivalent antimonial, potassium antimony tartrate (tartar emetic), was the first drug shown to be therapeutically specific in visceral leishmaniasis. Sodium antimony tartrate, which is slightly less toxic, is as effective and may profitably be used as an alternative to it These two cheap and chemically simple trivalent preparations of antimony *are still used where cost is a primary consideration, as in mass* treatment They suffer, however, from two major disadvantages; they are extremely irritant, and so must be given intravenously with meticulous care, and they cause some unpleasant, and very occasionally alarming and even fatal, toxic side-effects No other trivalent antimonial compounds have proved comparable to them in the therapy of kala-azar

A number of newer pentavalent antimonials are therapeutically effective in visceral leishmaniasis These compounds are much more costly, in view of their more complex chemical structure; they are not irritant, so they can be given intramuscularly as well as intravenously, and they are less toxic than are the simple trivalent salts, so a course of treatment with them can be completed within a shorter period

refractory to treatment Inadequate, or unsuccessful, treatment with antimony of any case of kala-azar subsequently renders that particular case of infection less amenable to it, a greater dosage of the metal becomes necessary to obtain even the initial response to it If successive sub-curative courses of antimony treatment are continued a stage ultimately is reached when the infection becomes completely refractory to antimony in the maximum tolerated dosage When a course of treatment with antimony is begun, therefore, it should whenever possible be continued to its completion without interruption Fortunately, when resistance to antimony is developed the infection remains susceptible to treatment with certain other drugs

An effective alternative to the antimonials, which is of particular value in cases of visceral leishmaniasis refractory to antimony treatment, is the diamidine series of drugs The diamidines are synthetic aromatic preparations which contain no heavy metal, they are therapeutically active against several protozoal infections of man and of animals Pentamidine isethionate, which is readily soluble, does not cause the troublesome neurological toxic side-effects produced by some other diamidines It is extremely effective in the radical cure of all forms of kala-azar, it is not effective in the treatment of post-kala-azar dermal leishmaniasis, which also is more refractory to the antimonials than is the primary visceral infection In cases proving refractory to repeated treatment with a variety of drugs, and with greatly enlarged spleens and hypersplenism, splenectomy followed by further intensive treatment may lead to cure

Advocated courses of treatment with a selection of the above-mentioned compounds are as follows

Sodium (or potassium) antimony tartrate – The drug is given as a 2 to 6 per cent solution in physiological saline, the solution must not be autoclaved as it then becomes unduly toxic. The injections must be given with the greatest care intravenously, serious sloughing may follow the escape of the irritant solution into the tissues For an adult the first injection is one of ½ grain of the drug; the second injection contains 1 grain; the third and subsequent injections each contain 2 grains of the drug The normal gross dosage of tartar emetic totals 25 to 35 grains of the drug; the doses are given daily or on alternate days

The toxic side-effects of tartar-emetic treatment during, or immediately after, each injection are a spasmodic cough, a feeling of constriction in the chest, pains in joints especially the shoulders, and, more rarely, syncopal attacks These can be minimized by giving each injection very slowly over a period of 10 to 20 minutes, the patient should be recumbent for each injection and should remain so for some hours after it Very occasionally irregularity in the temperature,

the serum, which also becomes solid and so resembles boiled white of egg, within two hours of performing the test. There are diminishing degrees of positivity down to a weakly positive formol-gel reaction, which is read when opacity but no solidification is evident within twenty-four hours of setting up the test. It is opacity which is the characteristic of a positive formol-gel test; solidification is not of importance in its interpretation The formol-gel test becomes positive within a month or two of the development of the disease, and it returns to negative after successful treatment and restoration to normal of the plasma proteins.

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especially with pentamidine, is often delayed The early stages of drug administration are commonly associated with an increase in the temperature and an exacerbation of the symptoms, and these may persist throughout pentamidine treatment The temperature then falls to normal, and shortly afterwards the spleen returns in size to normal with very remarkable rapidity, the abnormalities in the blood picture, especially the neutropenia, also rapidly disappear

Assessment of cure It is unwise to pronounce a patient to be cured of the disease until at least a year has elapsed after the end of treatment with no clinical or parasitological evidence of relapse

Post-kala-azar dermal leishmaniasis This condition does not respond to treatment with the diamidine series of drugs, and is more refractory to antimony treatment than is the initial kala-azar to which it is a sequel A full course of antimony treatment should therefore be given, and this may require repetition

MUCO-CUTANEOUS LEISHMANIASIS

DEFINITION

Muco-cutaneous leishmaniasis, or espundia, of South America is a condition due to infection of reticulo-endothelial cells, initially of the skin and subsequently of the mucosae of the mouth and nose, with the protozoan parasite *Leishmania brasiliensis* The infection is conveyed from man to man by the bite of certain sandflies (*Phlebotomus* spp), in which the parasites undergo a multiplicative cycle The resultant disease, after a variable incubation period, classically is characterized by the appearance of a variety of skin lesions, these commonly are papular, become nodular, and then ulcerate, later, metastatic lesions develop in the mucosae and these extensively erode the adjacent tissues The sepsis and mutilation resulting from the destructive lesions are responsible for much suffering and a considerable mortality This sequence of development is by no means invariable, the condition may not progress beyond the initial cutaneous lesions

GEOGRAPHICAL DISTRIBUTION

Classical muco-cutaneous leishmaniasis, due to *L. brasiliensis*, is confined to the lower altitudes of the continent of South America, where it occurs from coast to coast between 21° N and 30° S in well-defined areas It is limited to the hot, moist, afforested regions in which the vectors are abundant and is a sylvan and not an urban disease, it does not occur even in those parts of the endemic forest regions which have been cleared for settlement In these hot humid areas the majority of

muscular cramps, a rapid pulse and collapse occur during tartar emetic treatment; the appearance of such manifestations indicates the need for caution in continuing the antimony treatment or there may be a fatal issue

Urea Stibamine – This compound contains antimony in the pentavalent form, and it has been widely and successfully used in the treatment of kala-azar in India and elsewhere It is a mixture of urea and *para*-aminophenyl stibinic acid of inconstant constitution. The drug is given on alternate days intravenously; it is painful on injection into muscle The initial dose for an adult is 0 05 gm of the drug; the second is 0 1 gm, the third is 0 15 gm; the fourth and subsequent injections contain 0 2 gm of the drug A normal course consists of 15 injections Urea stibamine must not be boiled in solution, and it must not be left exposed to the air as it becomes toxic under such conditions

Pentostam (B W), Solustibosan – This is a stable solution of sodium antimony gluconate which contains 100 mgms of antimony, in the pentavalent form, in each cc The injections are given daily intravenously or intramuscularly. The adult dosage, after an initially smaller one, is 6 cc daily to a maximum of 12 to 14 injections; 6 or 8 injections suffice in cases of Indian kala-azar. For children the dosage is adjusted to the body weight, proportionally it may be higher than for adults, as children usually tolerate antimony well

Neostibosan (di-ethylamine *para*-aminophenyl stibinate) is another *effective pentavalent antimonial which can be given intramuscularly* or intravenously in doses of 0 3 gm There are several other pentavalent antimonials which may be used alternatively.

During treatment with the pentavalent antimonials a condition resembling anaphylactic shock sometimes occurs an hour or so after the fifth or the sixth injection. The temperature rises sharply, often with a rigor, and there may be an urticarial eruption, oedema, difficulty in breathing, cyanosis and severe shock, sometimes with a fatal issue. In the event of this adrenaline should be given at once and the reaction is treated on general lines Treatment should be resumed with caution using another preparation of antimony, initially in modified dosage.

Pentamidine isethionate. It is an aromatic diamidine compound of the following constitution – 4 4′-diamidinophenoxypentane di-(B-hydroxyethane-sulphonate) – and is issued as a powder in ampoules It is usually given intramuscularly but may be given intravenously though this causes a sudden fall in blood pressure The dosage is 10 to [illegible] is
d

The response to specific treatment of kala-azar with antimonials, or

due to proliferation of infected vascular endothelial lining cells. Pyogenic bacterial infection of the ulcerated area is followed by inflammatory changes in it. By a route not yet elucidated, metastasis of the parasitic infection of the skin takes place in the naso-bucco-pharyngeal mucosal surfaces, this causes foul ulcerative lesions which involve and destroy adjacent tissues causing distressing deformity.

CLINICAL PICTURE

As a rule the time intervening between infecting sandfly bites and the appearance of skin lesions on their sites lies between 10 and 25 days. The primary lesions are usually located on exposed parts of the body, they generally range from one to three in number but occasionally may be more numerous. These initial lesions commonly take the form of papules which burn and may itch, there is usually some enlargement of lymph glands of the group draining the area.

A considerable descriptive terminology has been applied to the various clinical forms these skin lesions may assume, and this only serves to emphasize their variety. The initial lesions may retrogress and vanish, or they may remain stationary without further apparent development. Alternatively they may become nodular tumours, which may or may not ulcerate.

The ulcerated type of nodular lesion is the most characteristic and common. The ulcers vary considerably in size, often exceeding 10 cm in diameter. They have sharply defined edges, and a much depressed base which lies on the structures beneath the skin, an indurated wall which projects above the level of the surrounding skin surrounds them. From the base of the ulcer there exudes a sero-purulent discharge, the surface of this usually dries and forms a tough brown membranous crust.

The non-ulcerating lesions are classified as being impetiginous or nodular (tuberiform). The latter may be verrucose or framboesiform, the second being the more common. The verrucose lesion is a firm wart-like tumour with a markedly irregular surface covered with an exudate which dries later into a hard scab. The framboesiform lesion is a soft papillomatous tumour resembling a yaw.

Regional lymphangitis and lymphadenitis may be associated with the development of the ulcerating skin lesions. Though the glands do not greatly enlarge, the lymphatics are very much thickened and cord-like, nodular dilatations in them may break down and ulcerate through the overlying skin forming new skin lesions.

The outstanding feature of *L. brasiliensis* infection is metastasis of the infection in the mucosae, commonly those of the upper respiratory tract and of the mouth are involved, rarely those of the genitals. Though

cases of infection progress to the metastatic stage In drier, colder areas this is rarely the case and the lesions remain cutaneous, without mucocutaneous metastasis

Espundia-like lesions of the mouth and nares have been recorded in the Sudan, and in other regions where *L. tropica* is the prevalent parasite

AETIOLOGY

Though *Leishmania brasiliensis* morphologically and culturally resembles *L donovani* and *L. tropica*, antigenically it is entirely distinct from either of these The parasite is introduced into man during the act of biting by infected sandflies Initially, in most cases, the infection appears to be confined to the skin, its appearance later in mucous membranes remote from the initial lesions suggests metastasis following the carriage of the organisms in the blood stream

The sandflies *Phlebotomus whitmani*, *P pessoai* and *P. migonei* are proven vectors in nature of *L. brasiliensis* in South America, on epidemiological grounds, and in view of the fact that it can be infected experimentally, *P fischeri* may be assumed to be a vector species. As in the case of *L donovani* and *L tropica*, the appropriate sandflies acquire the infection by ingesting Leishman-Donovan bodies when feeding near a lesion These, in the gut of the insect, become flagellate leptomonads which multiply rapidly and migrate forward to the pharynx and mouth parts of the infected insect The escape of flagellates into a wound at the time of biting is the means whereby the infection enters a new host.

The epidemiology of *L brasiliensis* infection suggests that there are animal reservoirs of infection Cultures of the blood of the spiny rat, *Proechimys semispinosus*, have yielded the organism, and were infective to human volunteers

PATHOLOGY

Leishmania brasiliensis enters the skin in the flagellate leptomonad form, it there multiplies rapidly in the form of inert Leishman-Donovan bodies which parasitize histiocytic cells in the infected area of skin A papule forms which develops into a nodular granulomatous tumour; this contains very large numbers of proliferating and parasitized cells of the macrophage type In association with the appearance of the earliest skin lesion there is some enlargement of the lymphatic glands draining the area; in these also are to be found many macrophage-type cells containing Leishman-Donovan bodies The skin tumours, which commonly are multiple, may remain small and in due course spontaneously disappear; or they may progress to a considerable size and, like Oriental sores, they commonly ulcerate following vascular obstruction

taken aseptically and cultured on suitable media will yield a growth of flagellates.

Montenegro's test is said to be positive in 95 per cent of cases. It is performed by injecting intradermally 0 1 cc of a phenolized suspension of flagellate leptomonads A positive reaction is read when a papule forms which reaches its maximum in 48 hours, persists for 4 or 5 days, and then disappears over the next 3 or 4 days.

There are no serological tests of practical value for the diagnosis of espundia

TREATMENT

The first record of the effective therapeutic use of tartar emetic was in the treatment of this condition by Vianna (1912) The subsequent adoption of tartar emetic for a variety of therapeutic purposes flowed from his announcement

While tartar emetic cannot be deemed a satisfactory specific for espundia it remains the most effective form of antimony for its treatment The dose for an adult is 0 1 gm intravenously; it is given on alternate days for 12 to 15 injections This course of treatment has to be repeated on several occasions, with intervals of a couple of weeks between each course Even though apparent healing of skin and of mucosal lesions may ensue, relapses with exacerbation of the lesions are prone to follow

Other trivalent antimonial preparations, such as Fouadin, are used but they are less effective The pentavalent antimonials are of no value in the treatment of this condition

Arsenic in the form of Eparseno (amino-arseno-phenol), which is a glucoside of arsphenamine dioxy-diamido-arsenobenzol is said to be the best drug available for the treatment of espundia It is prone to cause toxic side-effects, such as colic and diarrhoea, a skin eruption, and polyneuritis On the appearance of these treatment must be stopped The dose is 5 mgm per kgm of body weight and this is given intravenously or intramuscularly on alternate days for 10 days The course is repeated after an interval of 10 days, and it is again repeated on 3 or 4 occasions with similar intervals

Local treatment of the lesions includes cauterization with heat and diathermy, infiltration with solutions of emetine, mepacrine, berberine sulphate, phosphorated oil and other preparations

The non-metastasizing forms of *L. brasiliensis* infection rapidly clear with antimony treatment if this is given early and before they become chronic

it is conceivable that this metastasis may be due to autoinoculation it is generally thought to be the result of dissemination of the parasitic infection in the blood stream or through lymphatic channels Mucosal metastasis occurs even in those patients whose initial skin lesions have run an apparently abortive course. In about 10 per cent of all cases it makes its appearance early, and concurrently with that of the skin lesions; in the others it appears later and often after some years, as long an interval as 15 years has been recorded between the appearance of skin lesions and mucosal metastasis However, it has been shown that leishmanial infection of the nasal mucosa takes place long before clinical evidence of its presence is apparent in some cases; curettings of nasal mucous membrane have yielded Leishman-Donovan bodies some time before the mucosa underwent obvious changes The mucosa of the anterior part of the cartilaginous septum is that usually the first to change in appearance It becomes reddened, an ulcer forms, and this spreads and extends deeply into the surrounding tissues, all tissues, including cartilage but not bone, are destroyed. Adjacent and opposing mucosal surfaces become infected, and the process extends backwards into the nasal cavity Ultimately the entire cartilaginous framework of the nose disappears, the ulcerative process destroys the lips; it invades the soft palate, the fauces, and the rhino-pharynx; and in due course it extends to the larynx and the trachea. It causes much suffering, hideous mutilations, and gross deformities which may lead to death from respiratory involvement or from inanition due to inability to take food

The non-metastasizing forms of infection, which remain cutaneous, occur in cooler and drier areas and assume forms peculiar to the locality. Among these are 'uta', a dry form of skin lesion seen in Peru, a still milder form which is encountered in Guiana, Panama, and Costa Rica; and 'bay sore' or 'chiclero's ulcer' which occurs in Yucatan, Guatemala and British Honduras. The last of these is largely confined to the ear, and is common among chewing gum gatherers and mahogany tree cutters working in uninhabited forests over considerable periods

DIAGNOSIS

Recovery and identification of the causative parasite puts the diagnosis beyond doubt. Aspiration of tissue juice from the lesions in [illegible] esions, [illegible] eristic [illegible] these is so small that they cannot be recognized on microscopical search of smears stained with Leishman or with Giemsa's stain, similar material

leptomonads from the mouth parts of the infected insect into the skin during the act of feeding

Cutaneous leishmaniasis attacks non-immune persons of all races, any age, and either sex Among the indigenous populations of the endemic areas the lesions most commonly are seen in children This is because children, owing to their tender skin and their habits, are prone to be bitten by arthropods, and also because recovery from an infection affords substantial immunity to later reinfection Where the incidence of the disease is high most of the adult population have suffered from it in childhood, have recovered from it, and have subsequently enjoyed a material resistance to reinfection This development of immunity to reinfection has long been appreciated by some primitive peoples who deliberately infect young children on a thigh by contamination from a sore, with a view to forestalling a natural infection of the face with its resultant disfigurement Today it is common practice in certain parts of the Middle East to infect children of the upper classes, in the same manner, with living cultures of *L tropica* to the same end These artificial infections do not differ, except in site, from natural infections and are subject to the same complications, particularly in children, without the greatest care, the infection may be disseminated by contact with the opposing thigh, or by scratching to the face, the very area which the artificial infection was given to protect

PATHOLOGY

The pathological changes are limited to the points of infected skin The local reaction to the infection is the multiplication of macrophage cells in the area, and swelling and proliferation of the endothelial cells lining small vessels, both of which contain very large numbers of parasites Normally a small granulomatous nodule forms, this increases in size to that of a pea or larger, the damage to and proliferation of the lining cells of the vessels supplying it causes their obstruction, and this is followed by necrosis of the centre of the tumour An ulcer is thus formed, the cavity becomes infected with pyogenic bacteria, chronic mild inflammatory changes then develop, and a slight lymphangitis and lymphadenitis follow The leishmanial infection being a local one, gives rise to no remote or constitutional changes, the blood picture does not show any characteristic deviation from normal

CLINICAL PICTURE

The time elapsing between an infecting sandfly's bite and the development of the ensuing skin lesion at its site varies from a few weeks to as much as three years, usually it is between three to six months

The initial lesions always occur on a part of the body normally

CUTANEOUS LEISHMANIASIS

DEFINITION

Cutaneous leishmaniasis is a condition due to infection of reticulo-endothelial cells in the skin with a protozoan parasite, *Leishmania tropica* The infection is conveyed from man to man by certain sandflies (*Phlebotomus* spp) in which the parasite undergoes a multiplicative cycle The resultant disease is characterized by the presence of single, or multiple, indolent skin lesions on exposed surfaces of the body. These lesions are discrete and normally take the form of ulcerated tumours; there is no systemic involvement The infection spontaneously disappears, usually within a couple of years, leaving disfiguring scars

GEOGRAPHICAL DISTRIBUTION

Cutaneous leishmaniasis (Oriental sore, Delhi boil, Baghdad boil; Aleppo boil; Biskra button) occurs widely in the tropical and subtropical areas of Europe, Asia Minor, Asia, Australasia, and Central and South America It is of patchy geographical distribution largely being confined to regions with an arid climate and marked diurnal variation in atmospheric temperature, such as deserts. The vector sandflies belong to species which flourish under such conditions. The geographical distribution of cutaneous leishmaniasis extends much beyond that of the visceral disease (kala-azar); and the local distribution of the two is distinct. The insect vectors of each infection are peculiar to it

AETIOLOGY

In nature *L. tropica* infects a wide variety of animals; it is probable that in certain sparsely inhabited areas these serve as reservoirs of the infection, from which man acquires it In some animals, as in man, the infection is purely a cutaneous one, but in others it becomes systemic.

In man the parasite takes the form of the Leishman-Donovan body, which is found in reticulo-endothelial cells, macrophages and vascular endothelial cells in the skin lesions. Each lesion is the result of a bite by an infected sandfly, or of the transference of the L D bodies from an established sore to another site by contact, or mechanically by scratching, and their entry into abraded skin

The most important vector sandflies are *Phlebotomus papatasii* and *P. sergenti*, which become infected by feeding on the indurated walls of a sore The subsequent development of the parasite in the flies is similar to that of *L. donovani* in its appropriate insect vectors; the infection is later re-conveyed to a fresh host by the escape of flagellate

a thumb nail or larger It becomes grossly septic and, under such conditions, it at last heals spontaneously with much scarring; if on the face this causes a cosmetic deformity which in the vicinity of the eyes, mouth or nose, may actually be crippling

While single sores are most common in the cleanly and well cared for, multiple sores are usual in the poorer native population of an endemic area Nevertheless, two to three hundred sores distributed over the face, forearms and backs of the hands have developed on a European visitor after a short visit to a Middle East endemic area

In addition to this, the 'normal', form of Oriental sore, non-ulcerative verrucous or fungating types of lesions are seen to a lesser extent in the same areas of endemicity, these appear to be especially prevalent in south-eastern Russia and Turkestan In the latter areas the lesions assume a fungating papillomatous, or cauliflower-like, form without ulceration

On occasions an espundia-like condition, with progressing involvement of the mucosae of the mouth and nose, has developed as a sequel to an Oriental sore

DIAGNOSIS

The diagnosis is established when the causative parasite has been recovered and identified Before the sore reaches the stage of self healing Leishman-Donovan bodies are present in enormous numbers in its indurated walls and in the tissues underneath its base They will *not* be found by pulling the scab off the lesions and examining the underlying pus

A portion of the unbroken skin in the outer wall of the indurated tumour is cleansed, a fine needle on a syringe, or a capillary glass pipette with a compressed rubber teat, is pushed well into it and a tiny sample of tissue juice is aspirated The aspirated material is smeared on a slide, which is stained with Leishman's stain or by Giemsa's method If the clinical diagnosis is correct numerous intracellular Leishman-Donovan bodies will probably be found Material obtained in the same way, with strict aseptic precautions, is sown on a medium suitable for the culture of leishmania, this is maintained *at room temperature and is examined for up to three weeks before discarding* In the absence of bacterial contamination if leishmania were present in the inoculum there will be a growth of flagellate leptomonads within this time

TREATMENT

If Oriental sores are cleansed and are freed from pyogenic infection they tend to heal spontaneously and scarring is minimized Before any

unprotected by clothing and available to the attack of the flies The face, the forearms and backs of the hands, and the thighs, legs and dorsa of the feet are the most common sites in those wearing European-type tropical clothing The scalp is not involved even when unprotected Normally the lesion initially takes the form of a small red itching papule, this becomes a small nodule which is surrounded by a zone of erythema The centre of the granulomatous tumour then breaks down and an ulcer forms From this, when it is secondarily infected, there exudes a small amount of mucoid pus which dries and forms a crust The lesion increases in size; it becomes more indurated, and the area of ulceration correspondingly increases. The mucoid pus exuded from



FIG 21 Cutaneous leishmaniasis Oriental sore [From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

the ulcer base forms a leathery scab, in which sand, dirt and other particles become imbedded

The walls of an Oriental sore stand up above the surrounding skin, [illegible]

the presence of gross bacterial contamination If, however, the base of the lesion can gently be cleansed without causing bleeding some serous [illegible]

[illegible]

XIV

LEPROSY

DEFINITION

LEPROSY is a condition due to infection with *Mycobacterium leprae*, Hansen's bacillus The disease is characterized by a lengthy incubation period and a very chronic course during which lesions develop particularly in the skin and in peripheral nerves The mortality from leprosy itself is low, but intercurrent disease with a fatal issue is prone to supervene in those suffering from it

GEOGRAPHICAL DISTRIBUTION

There are records of the existence of what almost certainly was leprosy in India, China and Egypt many centuries before Christ From these countries it probably spread to neighbouring countries, and later it was disseminated widely throughout the world by movements of people during military, religious, or trading activities At the present time leprosy is chiefly a disease of the tropical and sub-tropical areas of the world, it has now largely disappeared from the temperate and colder areas It is prevalent throughout Asia and Asia Minor, in Africa, and in Central and South America, it also is found in southern Europe and around the Mediterranean littoral, in New Zealand and many Pacific Islands, and on the eastern and the western seaboards of Australia, it occurs autochthonously to a minor extent in more temperate and better developed regions of the world

The conditions said to favour its maintenance and spread are intimate human contacts in squalid unhygienic surroundings, particularly in a hot and humid atmosphere

AETIOLOGY

The causative organism, *Mycobacterium leprae* is an acid-fast bacillus which morphologically closely resembles that causing tuberculosis It differs from the latter organism in two important respects, it has not so far been maintained in culture, and it has not so far been established and maintained in experimental animals Furthermore in spite of many attempts, there is no occasion on which deliberate inoculation of the organism has led to the subsequent development of leprosy in man This failure to culture the bacillus or to maintain it in animals has greatly hindered expansion of knowledge of the infection and of its treatment Nevertheless, the organism is so consistently found in the

other treatment is undertaken every attempt should therefore be made to cleanse the lesion by fomentations, and by eusol and similar applications

Scraping with a sharp spoon and swabbing with pure phenol, under general anaesthesia, followed by strapping with elastoplast for a week or two may result in healing of isolated large sores Other means of physical treatment include local applications of solid carbon dioxide, or diathermy, or X-rays, or radium, any of these may prove satisfactory in individual cases

Infiltration of the walls and under the base of a sore with emetine hydrochloride, with mepacrine methane sulphonate, or with berberine sulphate may cause it to resolve The emetine hydrochloride is introduced in the form of a 5 per cent solution; 1 to 2 cc are infiltrated into and underneath the lesion. Berberine sulphate is similarly given as a 2 per cent solution, and the infiltrations with this drug are repeated on up to half-a-dozen occasions Berberine sulphate seems more effective than other drugs when locally filtrated in this manner.

There is thus no specific drug treatment for cutaneous leishmaniasis Antimony given parenterally, which is specific in visceral leishmaniasis, is not very effective in the cutaneous form of the disease due to *L. tropica* Its use by this route is justified only when multiple sores on a patient preclude the local treatment of each Antimony may also be applied locally to sores in the form of a 4 per cent tartar emetic ointment, this is very painful unless cocaine is incorporated in it; it is no more satisfactory than is antimony administered by the parenteral route.

PROPHYLAXIS

As already stated, in certain endemic areas it is the practice to infect the thigh of a child with cultures of *L. tropica* The resultant lesion may be a severe one, but if it is allowed to continue untreated for some time a substantial immunity to reinfection follows; this immunity is not complete, and there are records of reinfection of individuals who have had a sore some years previously.

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lesions in patients suffering from the progressive form of the disease that its specificity as the causal agent is now rarely questioned.

Source of Infection The skin and mucous membrane lesions in cases of the lepromatous type of leprosy contain enormous numbers of bacilli which may escape to the exterior; it is these cases which are the potentially infective cases of leprosy In the tuberculoid type of case the bacilli are extremely scanty, and so potentially such cases are much less infective to others.

Infection The mode of acquisition of leprosy is still in doubt; it is generally believed that the infection is acquired through the skin, particularly in childhood. Most adults are highly refractory to infection; children are much less so, but even in childhood long-continued intimate contact with infective cases of leprosy is probably necessary for the maintenance and spread of the disease in a community.

Development When the organisms establish themselves they multiply to a limited extent or vigorously according to the response of the tissues of the infected person to their presence In those patients in whom the local cellular reaction of the tissues to the presence of the organisms is vigorous their multiplication and dissemination are restricted, in those in whom there is no significant tissue reaction the organisms multiply rapidly and disseminate freely

The vigorous cellular response in some cases may succeed in localizing the organisms and eventually in destroying them without more general infection In others in whom the defence is rather less effective the organisms pass from the pars reticularis of the corium to other layers of skin and also through the terminal twigs of the cutaneous nerves to the nerve trunks In patients with no tissue response the bacilli readily pass into the small nerves in the corium, and thence ascend the nerve branches to the nerve trunks; in addition they freely spread locally, and they travel in the skin lymphatics to remote areas of skin. In explanation of the latter, the skin throughout its depth is freely supplied with lymphatics which directly intercommunicate through the skin of the entire body surface without passing through lymph glands. Bacilli and other particles of matter finding their way into these channels may slowly be conveyed to areas of skin anywhere on the body It appears that it is the terminal nerve twigs in the skin which are the site of election of *Mycobacterium leprae*, and it is now believed that their establishment and multiplication there constitutes the inception of clinical leprosy

PATHOLOGY

A study of the voluminous literature on leprosy shows much confusion and apparent contradiction in the accounts of its pathology. These arise from the extraordinary diversity of the clinical lesions

encountered in this disease, and from the previous inability of leprologists to agree on the identification and classification of the various types of lesions, and on their nomenclature Increasing understanding of the pathology and of the histology of the disease in its various forms is already doing much to resolve these difficulties

Types of Disease Fundamentally it at least is agreed that there are two extreme clinical types of leprosy The first of these is 'lepromatous' leprosy, which is associated with free multiplication of the causative organisms and their ready dissemination in the body without evoking any specific cellular reaction to their presence The second is 'tuberculoid' (or 'neural') leprosy, in which the multiplication of the organisms and their dissemination is restricted by an active defensive mechanism of the tissues locally, though there is no evidence of a generalized tissue or of a humoral body defence The first, or lepromatous, type of the

causative organism and its products The histological pictures characteristic of the lesions in these two extreme clinical types of leprosy differ widely In addition to those characteristic of these two extreme types some lesions intermediate between them may be seen, these are now called 'dimorphous' lesions The histology of the three forms of disease is described below

I *Pre-leproma* The initial and the earliest skin lesions in the lepromatous type of the disease on clinical examination show little departure from normal There are slight changes in the colour and texture of the affected skin, but the demarcation of the involved area is vague, and it is extremely difficult to detect its presence in a poor light It usually is slightly erythematous, and so is more readily seen in white-skinned patients than in coloured There is no change in sensation over the lesion This lesion is referred to as a 'vague' macule, or as a 'pre-leproma'

On histological section there is a slight, often negligible, generalized round cell infiltration of the corium of the affected area, the overlying epidermis is not involved, and it is clearly separated from the underlying infected corium by a narrow transparent zone of demarcation

bacilli are to be seen in the tissues outside the nerves during this pre-lepromatous stage Therefore ordinary clinical methods of search for the organisms, by shavings of the epidermis or incision into and

scraping of the corium, may fail to reveal their presence in the prelepromatous lesions.

Leproma. As the pre-lepromatous lesion progresses to the lepromatous lesion, bulbous or fusiform swellings containing dense masses of closely packed bacilli develop along the affected nerve twigs; slight lymphocytic accumulations, with some mononuclear histiocytic cells, appear around them. The swellings along the course of the nerve twigs rupture and liberate their contained bacilli into the surrounding dermis, where many are engorged by histiocytes. Histiocytes loaded with bacilli become globular and vacuolated; they degenerate to form Virchow's 'foam' cells; and these bacillus-loaded foam cells are characteristic of a lepromatous lesion. In addition, 'globi' form; these are masses often of considerable size, of bacilli tightly packed within a thin envelope; they, also, are characteristic of a lepromatous lesion. A constant feature of the histology of the lepromatous type of skin lesion is the restriction of any cellular or inflammatory reaction there may be to the pars reticularis of the dermis. There is no involvement of the overlying epidermis, which in sections is seen to be separated from the affected dermis by a narrow clear stratum free from cells. This clear zone between the epidermis and the dermis is absent from the tuberculoid type lesion of the skin, in which the epidermis as well as the dermis is involved.

II. *Pre-tuberculoid*. The initial and early lesions in the tuberculoid type of the disease are very sharply demarcated from the surrounding skin, from which they are readily distinguished on clinical examination. *The surface is firm and dry, and it may be hypo-pigmented.* Over it there is at first a diminution in, or an absence of, heat and cold sensation and appreciation of light touch; later there is complete anaesthesia and analgesia. The early lesion has variously been referred to as a 'simple' macule, an 'uncharacteristic' macule, or a 'maculo-anaesthetic' macule; the last is an appropriate descriptive term, but it might equally well be referred to as a 'pre-tuberculoid'. It does not extend nearly so rapidly, or metastasize as readily, as does a lepromatous lesion. On histological section it is characterized by the presence of [illegible]

nerve twigs and branches, many of which are degenerate.

Tuberculoid. As the lesion develops, branching granulomatous cords extend from the smallest nerve twigs in the papillary layer of the skin centripetally *downwards into the deeper dermis* and superficial subcutaneous tissues. These granulomatous 'tubercles' are composed of proliferating round cells and epithelioid cells; they involve the superficial nerve plexus, the non-medullated fibres supplying the arrector

pili muscles, the vasa vasorum of the muscular coats of vessels, the hair follicles and the sebaceous and the sweat glands. They extend steadily deeper into the skin invading and investing the nerves in each layer as they advance Very few bacilli at most can at any time be found in maculo-anaesthetic lesions, and it is unusual to recover them by the standard methods of examination

III. *Dimorphous* Patients with 'dimorphous' lesions may give a weakly positive lepromin reaction or a negative lepromin reaction The dimorphous skin lesions on clinical examination superficially resemble tuberculoids, they are less clearly demarcated from the surrounding skin than the latter, and they are more succulent and soft than are true tuberculoids On histological section dimorphous skin lesions resemble early tuberculoids, in that there is a massive infiltration of the corium with small round cells and epithelioid cells But in sections can be seen a clear zone between the epidermis and the underlying dermis which is characteristic of the pre-lepromatous and lepromatous type of lesion and is absent from tuberculoids, and the epidermis is not involved The later development of dimorphous lesions usually tends to be towards one or other of the extreme types, lepromatous or tuberculoid

THE SKIN LESIONS The pre-lepromatous lesions develop into 'macular', 'diffuse', or 'infiltrative', lepromatous skin lesions These clinical types of lepromatous lesion are not sharply differentiable one from another, but represent degrees of involvement of skin Histologically they conform in all essentials to the lepromatous lesion already described, their outstanding features are an abundance of bacilli in the nerve radicals and in the surrounding tissues, the presence of foam cells and of globi, and the absence of any marked cellular reaction, any [illegible]

The maculo-anaesthetic (or pretuberculoid) lesions, on the other hand, develop into 'minor' or 'major tuberculoids', here again the histological features conform in all essentials to those of the tuberculoid lesion already described They contain very scanty bacilli, and there is a vigorous cellular reaction of a specifically granulomatous nature, composed of epithelioid cells with giant cell formation

THE NERVE LESIONS It is evident from the histology of the skin lesions of leprosy that infection of the terminal nerve twigs by the organisms is invariable This infection is an ascending one from its initial establishment in the terminal nerve twigs in the skin through the nerve branches to the main peripheral nerve trunks, these are infected with organisms both in lepromatous and in tuberculoid type leprosy

The invasion of the peripheral nerve branches and nerve trunks by

large numbers of multiplying bacilli in the lepromatous type of disease is not associated with a commensurate tissue response to their presence The endoneurium becomes swollen and hyaline in appearance and contains numerous bacilli, but any cellular infiltration there may be is slight in amount and non-specific in character Nevertheless, there may be swelling of the nerve trunk during periods of exacerbation of the disease, and the pressure within the sheath of the acutely swollen nerve under such conditions causes much pain, and it results in damage to the component fibres finally producing a lepromatous neuritis.

The ascending invasion by scanty bacilli of the peripheral nerve branches and nerve trunks in the tuberculoid type of disease on the other hand is associated with a very vigorous cellular reaction; this is of a specific type comparable to that seen in and around the nerve twigs in the skin at the site of the pre-tuberculoid skin lesion As a result the nerve is markedly thickened by tumour formation; the pressure of the granulomatous tumour within the nerves destroys its component nerve fibrils, so causing marked secondary neural changes throughout the area of its distribution This is a tuberculoid neuritis which, in cases where doubt arises, can be differentiated from a lepromatous neuritis by means of the lepromin test On biopsy only few bacilli can be found in the affected nerve, and examination of serial sections may be necessary to disclose their presence.

Lesions of other tissues Other organs become invaded by leprosy bacilli, particularly in the lepromatous type of the disease. Those most commonly showing histological changes are the eyes and the testes. The eyes become infected with bacilli especially when there are lepromatous lesions in adjacent areas of the skin of the face. Alternatively, the eyes may be involved secondarily to damage to the nerves supplying the lids and the surface of the cornea in the tuberculoid type of the disease. Loss of the blink reflex and anaesthesia of the front of the orbit facilitate trauma and secondary infection; in many such cases ultimately there is loss of sight The testes are commonly involved in lepromatous leprosy; bacilli can be found in the seminal canals, the glandular tissue is damaged and secondary sexual changes, such as gynaecomastia, are by no means unusual.

CLASSIFICATION

The clinical manifestations of leprosy are dependent on the histology of the individual lesions It is desirable, as far as is possible, to determine the type of the disease as treatment and prognosis depend on its recognition The following classification has much to commend it, if only that it is rational, that it is adequately comprehensive, and that it accords with the known facts.

Major types of disease	*Tuberculoid*	*Dimorphous*	*Lepromatous*
Lepromin test	+ +	+ or — and may reverse	—
Skin lesions— Initial	Maculo-anaesthetic macule (pre-tuberculoid)	Atypical tuberculoid Atypical leproma	Vague macule (pre-leproma)
Later	Minor tuberculoid Major tuberculoid	Usually develops into leproma or into tuberculoid	Macular leproma Diffuse leproma Infiltrative leproma Nodular leproma
Neural Lesions	Polyneuritis		Polyneuritis

CLINICAL PICTURE

Incubation The incubation period of leprosy is very variable Lesions may appear weeks, months or years after the last contact with an infective case of the disease It is estimated that the incubation period commonly is about three years, occasionally it is only a few weeks, it is usually under five years, but it may be as long as twenty years

Onset The onset may be acute, with repeated attacks of fever, pains in peripheral nerve trunks, and the appearance of evanescent skin eruptions, in those patients who develop a very acute form of the lepromatous type of the disease Far more commonly it is insidious, and frequently it is not appreciated by the patient for some time As already stated, leprosy in a given patient tends to develop as one of two extreme types of the disease, the lepromatous in those whose tissues show little or no reaction to the infection, and the tuberculoid in those whose tissues react vigorously A dimorphous type of disease is also seen in which the subsequent development tends towards the clear characteristics of one or the other of the more extreme types, usually the lepromatous

In the majority of cases a skin lesion is the first sign, in some cases of tuberculoid type leprosy motor, sensory, and trophic lesions of an extremity are the first signs noticed The earliest skin lesions (pre-leproma or pre-tuberculoid) have already been described in the section on pathology Clinically, their differentiating characters are the sharp demarcation of the pre-tuberculoid lesion from the surrounding skin, as opposed to the indefinitude of the pre-leproma, and the obvious changes in appearance, in texture, and in sensation of the former. As the lesions slowly develop over some months the differences between them become still more clear Though bacilli can be obtained only

with difficulty, if at all, from the earliest lesions of either type, from the more advanced lepromatous lesion organisms can be recovered by the standard methods of examination (shaving of the skin, or incision into and scrapings from it) in great numbers. In addition to this, acid-fast organisms can be obtained in considerable numbers from lepromatous cases by scraping the mucosa of the nasal septum through a speculum. Organisms are rarely obtained from tuberculoid skin lesions, and none are recoverable from the nose in such cases.

TUBERCULOID TYPE LEPROSY

In a mild case of tuberculoid leprosy a well-defined local lesion may appear, persist for some weeks or months, and then spontaneously disappear without the development of any further manifestations of the disease Such cases are thought to occur particularly in primitive populations, and usually they are disclosed only when specifically sought for.

In other, more severe, cases of tuberculoid type leprosy the initial lesion persists, and other skin lesions later appear on the trunk and elsewhere Finally there is gross peripheral nerve damage, with the appearance of marked motor, sensory, and trophic changes, commonly in the extremities below the levels of the elbows and of the knees The tuberculoid type skin lesions take the form of minor or of major 'tuberculoids', the difference between these is one of degree and is governed by the extent and depth of the granuloma formation in the skin.

'Tuberculoids' are very sharply defined, are infiltrated, and are raised above the level of the surrounding skin, there is alteration in the appearance and the texture of their covering skin; and they are analgesic and anaesthetic Small nerves in their immediate vicinity are thickened and may be palpable, the larger nerve branches and the nerve trunks supplying them also commonly are thickened and palpable The skin over a tuberculoid is dry and scaly, often it is pebbled in appearance, and frequently it is depigmented; the sweat glands in it no longer function, and the deeper hairs in it fall out Tuberculoids may appear anywhere on the body, though, like all skin lesions of leprosy, they are rarely found on the scalp or other normally hairy parts

Tuberculoids sometimes become acutely inflamed and swollen, and even may ulcerate, the nerves supplying them are then swollen and tender This reaction is a local one and is not accompanied by fever or by any general systemic disturbance. It is held to be due to an acute exacerbation of the local tissue response to the infection; it is referred to as 'the reaction of recovery', and it is considered to be of good omen in that resistance to the infection manifestly is hyperactive

In the tuberculoid type of disease, as in all forms of leprosy, an

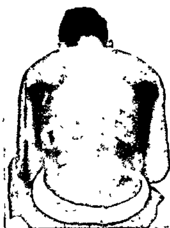


Fig 22 Tuberculoid lesions
[From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]



Fig 23 Claw-hand of tuberculoid type leprosy.
[From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

ascending invasion by bacilli takes place through the nerve branches to the peripheral nerve trunks, one or more of which become much thickened and readily palpable. The thickening is due to granulomatous tumour (tuberculoid) formation in the nerves in response to the presence of the organisms, whose multiplication is restricted by the cellular activity The cells invade and invest the nerve components and destroy its constituent nerve fibrils; increasing motor, sensory, and trophic changes consequently become evident throughout the area of distribution of the affected nerve trunk. This condition is the tuberculoid neuritis mentioned in the classification

A thickened ulnar nerve is easily palpable immediately above the elbow, and the thickening may be so marked that it is actually visible; the median and the radial nerves are as often involved as is the ulnar, but as they do not lie superficially the thickening in them is not readily detected. Destruction of components of the nerves in the forearm is manifested by anaesthesia and analgesia of the skin of the appropriate parts of the hand; paresis and wasting of the corresponding muscles, with eventually a drop wrist or claw hand; and trophic changes in all the tissues supplied by them The trophic changes cause the skin to become cold, shiny, and inelastic, and it no longer sweats; the palsied muscles become fibrotic and shrink, the bones become rarified, and the phalangeal bones usually become decalcified and may be absorbed The legs and feet suffer changes of a nature comparable to those seen in the forearms and hands. Thickened peroneal nerves can be felt, and may be seen, as they pass around the upper end of the fibula Collapse of the arches and eversion of an affected foot are common, and there may be drop foot

The insensitive and atrophic tissues are readily injured and become secondarily infected with bacteria 'Perforating ulcers' are prone to occur at points of pressure, for example under the heads of the metatarsals, under the os calcis, and on the palms These ulcers, if neglected, may become very deep and sinuses are formed to the underlying bones and other devitalized and infected tissues

Peripheral nerves other than those of the extremities may be involved The great auricular nerve commonly can be felt, and may be seen, to be thickened as it passes across the sterno-mastoids; facial palsies may develop, involvement of the innervation of the lids and eyes, with loss of sensation, of function of the orbicularis oculi, and of the protective blink reflex, leads to corneal ulceration and finally often to loss of sight Tuberculoid leprosy causes much mutilation and is a considerable cause of blindness where leprosy is endemic *It is paradoxical that in* this form of the disease, which is relatively benign in so far as progress of the causative infection is concerned, impairment of form and of function is greatest.

The tuberculoid tumours in peripheral nerve trunks may soften and caseate, forming nerve abscesses The increase in pressure resultant on these hastens the destruction of the surviving fibrils and so increases the secondary neural lesions in the tissues supplied by the nerves Abscesses are particularly prone to occur in the ulnar nerve above the elbow, and in the peroneal nerve below the knee and at other points where the affected nerves are flexed, pass beneath a fascia, or bend around a bone



Fig 24 Thickening of great auricular nerve in tuberculoid type leprosy [From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

LEPROMATOUS TYPE LEPROSY

The first evidence in most cases is the appearance of an indeterminate, vague and ill-defined skin lesion which persists and increases in extent It may occur on any part of the body This pre-lepromatous macule or 'vague' macule must be sought for in a really good light as it easily escapes notice The lesion is rather shiny and is slightly erythematous, it is flush with the surrounding skin, into which it blends without clear demarcation of its edges It is not anaesthetic It extends locally becoming a lepromatous macule, other lesions make their appearance in its vicinity and elsewhere, as the lesions extend many coalesce, and the areas of skin involved become very extensive The skin of the face and of the lobes of the ears commonly are affected early by macular, diffuse and infiltrative lesions of lepromatous leprosy The names applied to these lesions merely indicate the degree of involvement of the skin, the types are not clearly differentiable The skin becomes thickened by oedema and corrugated, especially over the supra-orbital, frontal, and malar bony prominences, so producing the classical 'leonine countenance' The eyebrows and the face are depilated, but the scalp is rarely affected

In addition to the diffuse and infiltrative types of skin lesion in lepromatous leprosy, nodular lesions may make their appearance These take the form of painless soft hemispherical intracutaneous or subcutaneous tumours which appear on any part but most commonly

are first seen on the ears and the extremities. They vary in number, and they range in size from that of a lentil to that of a walnut In some cases the nodules break down, ulcerate, and discharge matter containing enormous numbers of leprosy bacilli

The mucous membranes, particularly those of the nose, and as an extension from this of the mouth and upper respiratory



FIG. 25 Lepromatous type of leprosy, showing extensive infiltration, oedema and corrugation causing 'leonine countenance' Note depilation of eyebrows and face and thickening of ear
[From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

passages, are commonly involved in the lepromatous process; ulcers form and discharge innumerable organisms Secondary infection of the lesions can cause gross mutilation of the nose and nasopharynx, and of the larynx. Oedema of the larynx may require urgent tracheotomy.

When the skin of the face in the vicinity of the eyes is affected in lepromatous leprosy the organisms commonly find their way into the structures of the anterior part of the eye; the eyes become in-



FIG 26 Nodules in lepromatous leprosy
[From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

jected, there is engorgement and clouding of the media, iritis and other troubles develop, and the patient may suffer very severe pain in the affected eye.

The progress of lepromatous leprosy tends to be erratic; it is marked by exacerbations and apparent remissions. The exacerbations may be acute and be associated with a marked systemic and febrile disturbance, during these the existing lesions rapidly increase and new lesions make their appearance. This 'lepra reaction', or leprotic fever, may be comparatively mild and last only a few days, it may be very severe and persist for weeks and months. Lepra reaction is associated with rapid progression of the disease and further spread of the infection, it is therefore harmful, it must not be confused with the 'reaction of recovery' which is seen in a tuberculoid lesion, and which is a purely local reaction of immunity unassociated with any systemic upset. By careful treatment lepra reaction may be forestalled, injudicious treatment, and in particular the administration of iodides, is an effective method of precipitating it.

DIAGNOSIS

The unequivocal diagnosis of leprosy depends on recovery and identification of the causative organisms. In lepromatous leprosy this is usually easy, but in tuberculoid leprosy it is much less so.

LEPROMATOUS LEPROSY

Shavings of the skin above its capillary bed are taken from the crests of folds of skin pinched up over suspected lepromatous areas. The material is crushed and smeared on a glass slide, fixed by heat, and stained by the Ziehl-Neelsen method for acid-fast bacilli. Incisions are made with a fine (tenotomy) knife to the deeper fatty layer of the skin in the same areas. The incision is held agape, and material is scraped from its depth with the point of the knife and similarly examined for acid-fast bacilli. It is advisable to take a number of specimens by both these means from all suspicious areas of skin. In any but the earliest stages of the lepromatous disease organisms will usually be found without difficulty in some of the specimens.

activity of the disease present.

Smears of scrapings of the mucosa of the nasal septum taken with a curette or by means of a small swab-stick, also will show the presence of acid-fast bacilli in lepromatous leprosy. The recovery of acid-fast bacilli from this site alone should not be relied on for diagnosis, as there may be acid-fast organisms other than those of leprosy in the nose.

TUBERCULOID LEPROSY

Any persisting anaesthetic skin lesion, especially when associated with a thickened nerve trunk, in a person from a leprosy endemic region should be regarded as being possibly due to this form of the disease Skin shavings or incision smears, and nasal scrapings, may be examined, but they rarely yield organisms.

Where a peripheral nerve trunk can clearly be felt to be thickened, biopsy of the nerve should be done. Careful search of serial sections of he presence of

view of the gravity of its emotional and social complications, must never lightly or hastily be made Delay until proof, or at least reasonable certainty, is reached is justified by the chronicity of the disease and by its very low infectivity to others Patients with tuberculoid leprosy for all practical purposes are non-infective, even those suffering from gross lepromatous leprosy, and therefore potentially infective to others, do not constitute a danger to public health under good conditions of life

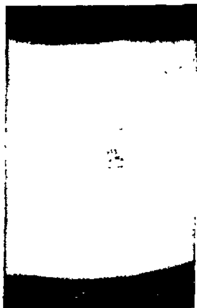


Fig 27 A late positive Mitsuda lepromin test in a case of tuberculoid leprosy

Lepromin (Mitsuda) Test The lepromin test is for a determination of the degree of sensitization of the skin to the leprosy bacillus or its products, it is not a diagnostic test for leprosy It is positive in those whose tissues react by specific tumour formation to the presence of leprosy bacilli, it is negative in those whose tissues do

tance in determining the type of leprosy from which a person may,

obtained from a patient suffering from active lepromatous leprosy.

The organisms are killed by heat or by other means A refined lepromin is obtained by treating the tissue with chloroform and ether, and then centrifuging at high speed The deposit is suspended in carbol-saline The test is performed by injecting 0 1 ml of the antigen intradermally, the site of injection is inspected after 24 hours, and daily thereafter There are other methods of preparing a suitable antigen from bacillus-containing material, and sundry modifications of the test

There are two types of positive lepromin reaction, the early and the late The early, the Fernandez reaction, appears within 2 days and fades by about the 4th day, the late begins at the end of a week and reaches a peak in 3 or 4 weeks It is the latter that is the classical Mitsuda reaction The early reaction is of the tuberculin type, there is an area of erythema half an inch or more in diameter, with some oedema and thickening. The late reaction is characterized by much local infiltration at the site of the injection, with the formation of a visible and palpable nodule which may undergo central necrosis

What is remarkable is that recently it has been shown that a similar test with antigen prepared from the skins of normal persons, never in contact with leprosy, gives closely comparable results, it seems to be just as specific as the classical lepromin test and its modifications

TREATMENT

LEPROMATOUS LEPROSY

Chaulmoogra For centuries the chaulmoogra oils, which are extracted from various species of *Hydnocarpus* and allied plants, were used in the treatment of leprosy The crude or the pure oils, ethyl esters of the oils, or salts of the contained fatty acids have variously been given orally, by inunction, intravenously, intramuscularly, subcutaneously, or intradermally Latterly it was usual for a portion of the selected preparation to be intradermally infiltrated into a lepromatous area of skin, the residue of the dose being injected subcutaneously or intramuscularly The chaulmoogra derivatives have also been injected into the tuberculoids of the neural type disease The consensus of current opinion is that the chaulmoogra treatment of leprosy was not specifically curative, and that any beneficial effect which follows its use was due to the local irritation and cellular reaction it provokes

The Sulphones Diaminodiphenylsulphone (D D S), or Dapsone, B.P C , was first synthesized in 1908 After the discovery in 1935 of the effect of sulphonamides on certain bacterial infections the possible therapeutic value of D D S. received attention In 1939 it was shown that the addition of D D S to culture media inhibited growths on them of human and of avian tubercle bacilli, its injection into rabbits infected with avian tuberculosis was found to modify the course of the disease in

these animals; but the drug, which is only slightly soluble, was thought to be too toxic for use in man.

Chemical elaborations of D D S. were then synthesized; these were thought to be less toxic than the parent substance but to retain its therapeutic activity One of these, Promin or Promanide, was first tried out in the treatment of leprosy in 1941. This compound was found to be too toxic when given orally, but, being more soluble than D.D S., it was successfully given intravenously in doses of up to 5 gms daily for some months to a number of patients suffering from lepromatous leprosy The progress of the infection in these was arrested, and in most [illegible] on over [illegible] ss toxic [illegible] is drug proved equally as effective as, and even superior to, Promin in the treatment of the lepromatous disease A number of other compounds followed, among them was Sulphetrone, which usually is given orally but which, with suitable adjustment of the dosage, can also be given parenterally Finally in 1947, in view of the growing conviction that all these synthetic derivatives exert their action by the liberation of the parent substance, D D S , the latter was introduced into the therapy of leprosy When given in suitably modified dosage by mouth D D S has been shown to be as therapeutically effective as its more expensive chemical elaborations; it is now being used extensively in the treatment of cases of the lepromatous disease in all parts of the world.

The defects of the sulphone treatment of leprosy are the extreme slowness of response to the treatment, the liability to reactivation of the disease if it is not sustained over at least some years, and the possible toxic effects of the treatment Nevertheless its introduction has very profoundly altered the outlook in all active cases, and in the early case the outcome is almost uniformly good.

Dosage of the Sulphones Whatever sulphone preparation is selected the drug must at first be given in very small doses The doses are cautiously increased over a period of at least two months to the full dosage for the particular preparation Failure to follow this course may result in the development of toxic side-effects in the form of gastrointestinal disturbances when the drug is given orally, and a severe anaemia with a marked reduction in the haemoglobin content and the red cell count; occasionally there is jaundice, rarely, a drug eruption, and sometimes a confusional mental state A death from agranulocytosis has been reported following treatment with diasone.

In addition to these toxic manifestations a lepra reaction (or leprotic fever) may be precipitated by over-vigorous treatment, or another condition referred to as *erythema nodosum leprosum*, which is akin to a Herxheimer reaction, may be the result of too vigorous treatment.

The former is an exacerbation of the disease, and is associated with fever, rapid proliferation of the organisms, and extension of the existing lesions with the appearance of new ones The latter is not due to lighting up of the disease, there is fever with the development of erythematous nodules, but the number of bacilli is not increased and indeed it may be diminished Although distressing this latter reaction is not of bad prognostic significance, indeed it is the reverse In either case the dosage at least must be reduced during the reaction, and thereafter it must again be increased with even greater caution

It follows that when giving the sulphones, particularly during the first few months, the patient must closely be watched, his temperature must regularly be taken, his blood picture must periodically be examined, and it is very advisable at regular intervals to re-assess the number of bacilli recovered by biopsy of his skin lesions

Diaminodiphenylsulphone – The maximum oral dosage of this drug at present advocated is 600 mgm per week It is given as 50-100 mgm daily for six days of the week, or up to 400 mgm may be given as a single dose twice a week Children tolerate the sulphones well, they are dosed proportionately to their age, a child of twelve being given half the adult dose

Diasone – It is put up in palatable tablets for oral administration From 0 6 to 1 0 gm may be given thrice daily, the maximum weekly dosage is 21 gm for an adult

Sulphetrone – By mouth a total of 21 gm per week is the maximum dosage desirable, this is given in the form of 3 gm in tablets daily For parenteral use the drug is given as a 50 per cent solution in water, up to 0 3 gm thrice daily can be given by this route

Thioureas – The thiosemicarbazone 'Thiacetazone', a monosubstituted thiourea, often produces a rather more rapid clinical and bacteriological response than does D D S during the first year of treatment During the second and third years, however, this is not sustained and deterioration sometimes sets in with a suggestion of the development of drug-resistance by the organism The patients, fortunately, show no loss of response to D D S treatment when this is substituted

Disubstituted thioureas, notably diphenyl thiourea (D P T), also have been on trial for some years with very promising results There have been no toxic side effects and no suggestion of the development of resistance to this drug in those treated, the results compare very favourably with those obtained with D D S treatment

Other compounds – The importance of alternatives to the sulphone series of drug is obvious In view of the similarity of the leprosy to the tubercle bacillus the antitubercular drugs naturally come in for consideration, but it does not follow that drugs effective against the one are

effective against the other. Isoniazid has proved disappointing when given alone; this may be due to the rapid development of fastness to it. When given with D.P.T to a series of patients over a period of one year the response to these two drugs has been very good.

P.A.S. has not proved to be of value. Streptomycin and dihydrostreptomycin are effective, but less so than the sulphones; their cost precludes their use on a large scale.

Diethyl dithiolisophthalate (ETIP or Etisul), a yellow oily liquid smelling of garlic, shows activity against tuberculosis even when rubbed [illegible]

thereafter evidence of resistance to the drug develops. Combined treatment with ETIP (3-6 cc twice weekly by inunction for 8-12 weeks) and D.D.S. (sustained) promises a more speedy response and recovery, with *shortening of the course of intensive treatment. The pungent smell of* ETIP is a serious disadvantage, which can be partly masked by scenting; the drug is cheap and it is nontoxic.

Without animal and culture infections the selection of drugs for examination is empirical. The assessment of their value is especially difficult in a variable and chronic disease; and all experimental work on man must be subject to ethical considerations, more particularly when dealing with such a disease.

THE DURATION OF TREATMENT

This under varying conditions of life and circumstances is governed by some imponderable factors; as a general rule specific treatment in lepromatous leprosy should be continued with or without intermissions certainly for many months, preferably for several years, and desirably for the remainder of the patient's life. Steady regression of the physical signs of acute lepromatous leprosy is almost invariably apparent after a few months' treatment with the sulphones, and it may continue until many or all of the skin lesions are no longer discernible. The number of recorded cases in which bacilli have first become fragmented and dust- [illegible]

Neglect of further treatment commonly is followed by recrudescence of the disease.

COMPLICATIONS

The acute ocular complications due to lepromatous invasion of the

tissues of the eye usually respond satisfactorily and rapidly to sulphone treatment, aided by suitable general treatment of the eye condition such as frequently repeated dilation of the pupil The mucous membrane lesions clear rather earlier under this treatment than do the skin

The treatment of lepra reaction in lepromatous leprosy has always proved a serious problem Conventionally, antimony was given but with dubious benefit The use of cortisone now affords a much more effective solution Cortisone also is of benefit during the local 'reaction of recovery' which may occur in lesions of the tuberculoid type of disease It should be given in conjunction with sulphone treatment, with a reduction in the dosage of the latter as deemed necessary

Cortisone has proved invaluable for the relief of most of the acute and serious complications of lepromatous type leprosy For example the distressing results of eye involvement are relieved by its use, and permanent tissue damage is thereby lessened Specific chemotherapy must be continued with it as the effect of cortisone treatment alone is only temporary

TUBERCULOID LEPROSY

Local reaction in the tissues to the presence of bacilli in the tuberculoid-type disease is vigorous, and the number of bacilli to be found in them is small, it may be so small that none can be found The need for chemotherapeutic destruction of the organisms in this form of the disease is therefore less than in the active infection of the lepromatous type disease, indeed it may be unnecessary to attempt it The age of the patient, the clinical picture, the progress of the disease, and the presence and numbers of the organisms recoverable by the recognized methods of examination will decide which patients do need specific treatment, this is then given as for the lepromatous disease

GENERAL

Concurrent infections, such as malaria, intestinal helminthic infestations, kala-azar, and many others prevalent in leprosy endemic areas, should if possible be eradicated The secondary neural lesions consequent on nerve damage cause palsies, deformities, and trophic changes Lack of sensation facilitates trauma, and secondary sepsis readily follows Every attempt should be made with proper orthopaedic assistance to minimize deformity Claw hand, for example, should not be allowed to develop, proper protection, by means of well-fitting soft footwear and a metatarsal bar on the shoe, will minimize the risk of perforating ulcer formation under the heads of the metatarsals Sepsis and ulcers should be conservatively treated, by cleansing with mild antiseptics and the use of antibacterial agents Surgery for amputation of digits, and even of limbs, may sometimes be necessary, but it should

never be undertaken either hastily or lightly. Tendon transplants of undamaged muscles, and similar orthopaedic operations, can do much to relieve deformity and to restore function in some cases when the progress of the disease is arrested.

Nerve pains may be severe in both the lepromatous and the tuberculoid type of disease. These are usually due to pressure within the nerve sheath; incision of the nerve sheath and stretching of the nerve trunk, or drainage of a caseating tumour if present in the nerve, may be necessary.

Lesions of the nose, mouth, pharynx, and throat should receive attention by suitable local application. Tracheotomy may be necessary when there is oedema of the glottis.

PROPHYLAXIS

The prevention of child infection should be regarded as a foremost aim in any campaign against leprosy. This ideally means exclusion of children from contact with cases of the lepromatous type of disease. The attempted compulsory sequestration of patients with leprosy in institutions has universally proved ineffective; it leads to concealment of the disease. A measure of partial isolation, in the form of the voluntary night segregation of patients suffering from the disease, has proved acceptable and reasonably effective in village communities.

Leprosy is not transmitted congenitally; a new born infant should therefore be removed at birth from an infective mother, and from the surroundings in which she lives, if left with its mother it will almost certainly contract the disease.

Most adults are largely immune to infection, and they are most unlikely to acquire it by casual contact.

XV

LEPTOSPIROSIS

DEFINITION

WEIL'S disease, spirochaetal jaundice, mud, field or swamp fever, and Japanese seven-day fever are among the names applied to diseases of man all due to infection with species, or races, of spirochaetal organisms belonging to the genus *Leptospira* These organisms occur commonly in rats and other small animals, and are found in stagnant water The infection of man is incidental, and often occupational, following contamination of the skin or mucous membranes or the pollution of food stuffs, usually indirectly, with the urine of infected animals The resultant disease when severe is characterized by fever, toxaemia, jaundice, haemorrhages, nephritis and albuminuria The mortality in some forms of infection is high

GEOGRAPHICAL DISTRIBUTION

World wide in its incidence, leptospirosis occurs irrespective of the climatic conditions

AETIOLOGY

There is doubt as to the validity of some of the many named species of *Leptospira* All morphologically are identical, their differentiation has been based on their pathogenicity to experimental animals, their serology, their virulence and the epidemiology of the local diseases they cause in animals or in man Serological tests indicate that the antigenic composition of the leptospiral organisms, and their agglutinogenic characters, are sufficiently constant for their classification By cross absorption tests the individuality of many distinct serotypes has been established with reasonable accuracy The type species of the leptospiral organisms is *Leptospira icterohaemorrhagiae*, and this organism is particularly associated with *Rattus norvegicus* as its carrier host Within some serotypes, for example *L icterohaemorrhagiae*, there are subtypes which in this particular case are designated A and AB respectively The number of leptospiral serotypes and subtypes so far identified is about 40, and this will doubtless rise Their distinction and differentiation patently are matters for a highly specialized laboratory and skilled staff

The leptospiral organisms are slender closely wound spirochaetes which vary in length from 8 μ to 24 μ The spirals are shallow and regular, each being about ½ μ in length, thus an organism of 7 μ long has over twenty spirals They are very pliable and are actively motile,

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tiply and are widely diffused in the blood stream throughout the body They tend to become localized in certain tissues, especially in the kidneys, liver, meninges, and sometimes the lungs They enormously increase in number during the first two weeks, thereafter they gradually disappear Apparently toxins liberated from dead spirochaetes cause changes in small blood vessels, resulting in focal haemorrhages and degenerative changes in the parenchymatous organs

At autopsy the body may or may not be jaundiced, there are small haemorrhages throughout the tissues, especially the muscles, lungs and kidneys The liver may be enlarged, and on section many glandular cells are found to be necrosed, the damaged cells are isolated and irregularly distributed, they are not found in masses, so the columns of cells in the liver lobules may appear rather irregular or dissociated There is no fatty degeneration of the liver The cause of jaundice is a hepatitis, commonly there is a secondary biliary obstruction and haemolysis On recovery the parenchymal cells rapidly proliferate to replace those destroyed and the liver form and function are restored

The kidneys are swollen and show multiple small haemorrhages On histological section there is a diffuse distal tubular necrosis, akin to that following crush injuries As in the case of the liver, on recovery regeneration of the epithelium restores the kidneys to normal, though in some few cases the lesions may progress to a chronic nephritis Sometimes the renal damage is so extensive that there is anuria with death from uraemia

CLINICAL PICTURE

The incubation period of Weil's disease ranges from four to nineteen

third that of convalescence

The onset of Weil's disease usually is sudden, with rigors and a sharp

are present, there may be petechiae, herpes labialis is usual, and the vesicles become haemorrhagic The tendency to bleeding in all tissues is shown by epistaxis, blood-staining of the sputum, and the presence of red cells in the urine The urine contains much bile pigment, there is always albuminuria, there is oliguria, there may be casts and blood cells

their extremities commonly are bent into a crook. In films they stain well with the Romanowsky dyes, and by silver impregnation methods They can readily be cultured on a variety of simple media, such as Noguchi's leptospira medium.

L. icterohaemorrhagiae in nature has been found to cause disease in primates, dogs and foxes, and possibly cats; it is readily inoculable into guinea pigs It occurs enzootically in rats, voles and field mice, and many other small rodents and wild animals; these may harbour the organisms in nature for prolonged periods without obvious ill-effect. The organisms invade the kidneys of these animals and are passed in their urine, they constitute the normal reservoir of infection Man usually becomes infected by consuming foodstuffs contaminated by the excreta of infected rodents, or more commonly by the entry of the organisms through skin or mucosal surface abrasions when working in contaminated damp places. Occupational outbreaks, or sporadic cases, of Weil's disease occur from time to time in men working in rodent-infested surroundings, particularly in sewers, canals, mines and tunnels, swamps and paddy fields, farmyards, and other places liable to contamination with rat urine

Canicola fever is an enzootic disease of dogs associated with nephritis but not with jaundice It is due to infection with *L. canicola*; this organism also at times affects man, in whom it causes a mild form of disease, but it has not been found in rodents; dogs are believed to infect one another through the urogenital tract and the urine Guinea pigs are refractory to infection with *L. canicola* but young hamsters are suscep-

nephritis

L. hebdomadis causes a very mild form of leptospirosis in man chiefly in Japan The disease occurs in agricultural labourers, and the reservoir of infection is the vole, *Microtus montebelloi*

L. grippo-typhosa causes the swamp fever of eastern Europe The reservoir of infection is presumably the rat. The disease in man resembles an intestinal form of influenza, and jaundice rarely occurs during it.

Leptospira biflexa is an organism almost universally present in stagnant water, immersion in ponds has not uncommonly resulted in an attack of Weil's disease, though of course this is due to contamination of the water by infected rodents

PATHOLOGY

The organisms gain entry to man through the uppermost alimentary, respiratory, or other mucosae, or through the skin They rapidly mul-

If the animal is then killed leptospira can be found in smears or sections of the liver, or by culture of the blood.

Agglutinins appear in the patient's blood about the sixth day and reach a maximum titre after the third week of the disease. Titres as high as 1/10,000 to 1/30,000, when tested against stock cultures, are commonly reached; the agglutinins may persist in the serum for years.

The agglutination test is made with a formalinized culture of *L. icterohaemorrhagiae* incubated with varying dilutions of serum for 18 hours at 37° C. The results are read by examining drops with dark field illumination under a microscope, the highest dilution to show agglutination of approximately half the leptospira is taken as the titre of the serum. With satisfactory controls, a positive reaction in a dilution of 1:20 is diagnostic. Zones of inhibition are prone to occur in this test, it must therefore be set up in a full range of dilutions.

The Brown and Davies adhesion test is an application of the Reichenberg phenomenon. One volume of 1:5 dilution of the patient's serum is mixed with one volume of a young actively-motile leptospiral culture, to these are added one volume of a suspension of *B. coli*, and one volume of a 1:5 dilution of fresh guinea pig serum. The whole is incubated at 37° C for 30 minutes, and a drop is then examined microscopically with dark ground illumination. When the test is positive the *B. coli* are seen to be firmly adherent to the leptospira.

TREATMENT

Antisera have been prepared by the immunization of large animals, such as the horse. These if given early, repeatedly and in large doses may favourably modify the course of the disease.

The antibiotics penicillin, aureomycin and terramycin if given in substantial dosage early in the disease are said to shorten its course and modify its severity but they must be given before the fourth day to be of any value.

Specific treatment of the infection is therefore at present of dubious value. There remains the need to combat the effects of the disease, of these renal failure is the most important.

and in very severe cases there is anuria. There is usually some anaemia, and there is an early leucopenia followed by a polymorphonuclear leucocytosis, with a total leucocyte count of 10,000 to 15,000 and in severe cases to 25,000 or more. The sedimentation rate is always raised

albuminuria gradually disappear, and recovery is complete by the fifth or sixth week. In about one third of the cases, when convalescence is beginning during the third week, the temperature suddenly rises to a high level. This 'after-fever' may persist for from four to twenty days; it is not associated with a recrudescence of the classical symptoms and

relapse of the Weil's disease, but to be a form of immunity reaction

Attacks of Weil's disease vary very greatly in severity. The degree of jaundice is an index of the virulence of the disease. Some are very mild and there is no jaundice; others are of the severity described; and yet others may be of fulminating intensity, with severe toxaemia, delirium, meningeal and nervous symptoms, and cardiovascular failure with death. Death occurs most frequently during the second week The mortality has varied greatly in the different recorded outbreaks; in British cases it is usually below 20 per cent, but in Japan it may be 50 per cent.

DIAGNOSIS

Initially it may be impossible to distinguish Weil's disease from infective hepatitis, yellow fever, or relapsing fever, on clinical examination. During the first week or ten days leptospira can be recovered from the blood by the following methods:

1 *Schuffner's triple centrifugation*: Spin 2 or 3 ml of citrated blood at 1500 r p m for 5 minutes, remove the supernatant fluid and again spin this fluid at 1500 r p m. for 10 minutes; again remove the supernatant fluid, add saponin to this fluid to a concentration of 1 in 1000, and spin at 3000 r p.m for half an hour Examine the deposit microscopically with dark ground illumination.

2. *Blood culture* Inoculate some drops of the blood on to a modified Fletcher medium This is made by diluting 0 5 ml of Lemco broth, pH 7.4, with 3 ml of distilled water and, after autoclaving, adding 0 25 ml of inactivated rabbit serum passed through a Seitz filter. Incubate at 30° C, and examine in three or four days

3 *Animal inoculation*: Guinea pigs inoculated intraperitoneally with infected blood suffer from fever and jaundice during the second week.

males in the tropics, and one called 'esthiomène' has for long been known to occur in Marseilles prostitutes These conditions are now known to be lymphopathia venereum

PATHOLOGY

The small primary lesion, which usually is seen only when it occurs on the external genitalia, is very superficial and consists of an infiltration of the subepithelial layer with mononuclear cells, lymphocytes, plasma cells and histiocytes, with a few polymorphonuclear leucocytes The endothelial cells of the small blood vessels of the affected area swell and obstruct them, as a result there is central necrosis in the lesion and a small shallow ulcer forms in it

The virus passes up the draining lymphatic channels to the associated

[illegible]

phonuclear leucocytes Focal abscesses develop where there is epithelioid transformation of the macrophages, and the resultant tubercle-like nodules undergo necrosis These slowly developing, irregular, or 'stellate', abscesses in the lymph glands are characteristic of the infection Those stellate abscesses near the surface of the gland discharge into or through the adjacent tissue, so forming sinuses Those deeper within the gland may be secluded by proliferating connective tissue, and eventually may be replaced by fibrous tissue

There is an intense connective tissue reaction around the affected glands, which become firmly adherent to the neighbouring structures

[illegible]

virus of the lymphatic vessels and glands

CLINICAL PICTURE

The incubation period is from a few days to two or three weeks, usually it is about a week

The primary lesion is very small and it is painless, it rarely lasts for more than a week, and as a result it is often overlooked In males it is usually located on the coronal sulcus, but it may be on the glands, on the prepuce, or within the urethra At first it is a papule about the size of a

XVI

LYMPHOPATHIA VENEREUM

DEFINITION

LYMPHOGRANULOMA INGUINALE, climatic bubo, poradenitis nostras, or Durand-Nicolas-Favre disease is a venereal disease due to a virus. It is characterized by an insignificant primary lesion followed by an associated lymphangitis and lymphadenitis, and usually some systemic upset. The affected lymph glands tend to undergo multiple focal suppuration with the formation of sinuses. In women with involvement of the lymph glands within the pelvis great deformity of the pelvic organs may result. The mortality is very low.

GEOGRAPHICAL DISTRIBUTION

World wide in distribution, it is most common in the warm climates and more prevalent in the coloured races than the white.

AETIOLOGY

The causal agent is a virus which very closely resembles in size, morphology, and staining characteristics those causing psittacosis and trachoma. The virus particles, as judged by passage through gradocol membranes, measure from 120 to 180 mμ. The virus is readily destroyed by environmental changes and by weak antiseptics; it will retain its viability for long periods when kept at −70° C. It can be cultured in living tissue cultures, and on the yolk sac of the developing chick embryo. It can be introduced into monkeys, mice, guinea pigs and less readily into other animals, locally by inoculation of infective material but can only be maintained for one or two passages by this means. It cannot be introduced into birds, and by this fact can be readily distinguished from the psittacosis virus. It can readily be maintained serially in some animals, in particular mice, by intracerebral inoculation, when thus introduced the virus causes a characteristic meningo-encephalitis. In nature the virus has been recovered solely from man.

The infection is usually transmitted venerally, and the disease it causes is detected much more frequently in males than in females. This may be due to the fact that in women the primary lesion is often con-

throat, sometimes with ulceration of the pharynx and tonsils In some [illegible]

In those cases in which later there is extensive destruction of the lymph glands and surrounding tissues there may be a secondary elephantiasis of the pudenda or of the legs Rarely, in the case of a purely external genital infection such as is usual in males, the virus infection may travel from the inguinal glands to the iliac glands In women in whom the primary lesion is intra-vaginal the virus is conveyed directly in the lymphatics to the pelvic lymph glands Suppuration and sinus formation in these glands extend into the neighbouring pelvic organs, and the virus infection may be further diffused into the other glands within the pelvis The sinuses cause fistulation of the vagina, rectum and other viscera, secondary bacterial infection results in chronic inflammatory and fibrotic lesions which involve and damage extensively the contents of the pelvis There is adhesion and fixation of the pelvic organs, there commonly are elephantiasis of the external genitalia, strictures of the urethra, vagina and rectum, tumour formation and various ulcerative lesions, recto-vaginal or urethro-vaginal fistulae, or even the production of a cloaca into which the rectum, vagina and urethra all open This progressive, chronic and disabling condition is known as the genito-ano-rectal syndrome, or esthiomène For obvious reasons it is much more prevalent in women than in men, but it is sometimes encountered in the latter when the primary seat of infection is rectal

DIAGNOSIS

Of the various methods devised for diagnosis of the disease the most conclusive is isolation of the virus This is best done by the inoculation of pus, aspirated from a bubo, intracerebrally into mice or monkeys, in which the virus causes a characteristic meningo-encephalitis Less effectively, the virus can be isolated by inoculation of the material on to the yolk sac of a developing embryonated hen's egg

The Frei skin test is an allergic test of much clinical value in the diagnosis of lymphopathia venereum It is performed by injecting into the patient intradermally an antigen containing heat-killed virus An antigen may be made from pus aspirated from the unopened stellate abscesses in the inguinal glands of a case of the disease The antigen most free from impurities is that made from cultures of the virus on the yolk sac of the chick embryo, it is now available commercially under the name 'lygranum' The test is read at 48 hours and 96 hours after the injection of 0 1 cc of the antigen into the skin of the patient, and preferably also into a normal uninfected control If positive, there is an

pin's head; in the centre of this there soon forms a shallow ulcer which has clear-cut edges The herpetiform ulcer is surrounded by a reddened zone; it is not indurated and it does not itch.

rectum Extra-genital sites of primary infection occasionally have been recorded.

In males, and in women who acquire a primary lesion on the external genitalia, there is a feeling of stiffness and an ache usually in one groin after ten to thirty days A single gland becomes enlarged, and can be

freely movable. If the patient is kept at rest it may subside and vanish within about a week, and there is then no further development



Fig 28 Lymphopathia venereum with unilateral inguinal adenitis

Usually the infection spreads from this first to the neighbouring glands of the group, and they also enlarge. The affected glands as a result of periadenitis become adherent to one another and to the skin and to the underlying tissues. Eventually the group forms a large lobulated oval or sausage-shaped mass, over which the adherent skin is shiny and purplish in colour. The lymphadenitis usually is unilateral but it may be bilateral. Resolution may occur even at this stage; but more commonly multiple small stellate abscesses form in the glands These increase in size and tend to fuse; those which are super-

mucoid pus, this at first is bacteriologically sterile The discharge from the fistulae continues over many weeks or months; eventually the condition subsides and healing takes place with scarring

Early in the disease, when the lymph glands are first becoming involved, there may be a febrile constitutional disturbance lasting a week or two This is rarely severe, but it may be associated with a sore

XVII

MALARIA

DEFINITION

MALARIA is a disease caused by sporozoa of the genus *Plasmodium* It is characterized clinically by fever, which is often periodic, varying degrees of anaemia, splenic enlargement, and various syndromes resulting from the physiological and pathological involvement of certain organs including the brain, the liver and the kidneys

GEOGRAPHICAL DISTRIBUTION

Malaria is probably the most widespread of all diseases It is found in regions lying roughly between latitudes 60° N and 40° S The distribution of the plasmodial species is not uniform Vivax malaria is widespread in the tropics and subtropics, and in some temperate regions Falciparum malaria is found most commonly in warm moist climates It is found in parts of Europe, for example the Balkans, Italy and Sicily, where it is seasonal in incidence It is found in most of tropical Africa, in Asia Minor, in parts of India and the Pacific area In many of these regions it is the predominant form of malaria present Malariae malaria occurs throughout the tropics, chiefly in Africa, South America, India, Ceylon and Malaya It is not as common as either vivax or falciparum malaria Ovale malaria is uncommon, it occurs mostly in East and West Africa and in South America

AETIOLOGY

Malaria attacks man at all ages and affects the sexes equally No race is immune, but repeated infection with a strain of plasmodium may result in the development of some immunity In immune individuals the disease is nearly always milder than in non-immunes infected in the same region

TRANSMISSION

The females of certain species of anopheline mosquitoes are the definitive hosts, man is the intermediate host Infection is normally transmitted to man by the bite of an infected mosquito but may occasionally occur across the placenta The disease may be induced artificially by injection of either sporozoites or trophozoites

Malaria may exist where the following conditions for transmission

infiltrated inflammatory dome-shaped swelling at least half a centi-*metre in diameter, which can both be seen and felt. In the centre of the* swelling there may be a small area of necrosis surrounded by a red zone The nodule often persists for from two to three weeks.

The Frei test almost invariably becomes positive one to three weeks after the development of adenitis. False positive reactions are very rarely encountered; but as the antigen contains a heat-stable component common to the psittacosis, trachoma, and some other viruses, a positive test might be accounted for by infection with one of these. *Once positive the test remains so for a very long time, and possibly for* the remainder of the patient's life. The interpretation of the Frei test therefore must be made in the light of the immediate clinical and other findings

An effective complement-fixation test, which also is group specific, can be performed in virus research laboratories.

TREATMENT

Complete rest in bed should be insisted on if the disease is diagnosed in the early stages Under this measure alone a case of external genital infection may be arrested and may spontaneously resolve at any stage of its development before fistula formation has occurred. If at this time softening can be felt in the affected glands, indicating stellate abscess formation, these should be aspirated under strict aseptic precautions to *forestall spontaneous fistulation*

If the enlarged glands do not begin to subside after a week or so on bed rest, but continue to enlarge, complete and clean surgical removal of the affected inguinal glands will terminate the condition Under no circumstances must the glands be incised, or there will be an indolently discharging granulomatous wound for many months, which finally will only heal with great scarring

The sulphonamides and the *antimonials given parenterally* have been claimed to effect a cure of lymphopathia venereum In practice their employment proves disappointing, and it is difficult to ascribe

is 0 5 gm six-hourly for ten days, and the desirability of complete bed rest with the drug treatment should not be overlooked Chloramphenicol is actively destructive to this virus *in vitro* and may prove to be of therapeutic value.

The treatment of the manifold complications encountered in the genito-ano-rectal syndrome, following pelvic involvement, after initial antibiotic treatment is palliative and surgical

haemozoin, formed by combination of hoematin and denatured pro- [illegible]

rupturing of the infected erythrocytes and consequent escape of merozoites is known as *sporulation*

Merozoites are either destroyed in the plasma or enter erythrocytes In the majority of freshly infected erythrocytes the asexual cycle is repeated but in some the sexual forms, the male and female *gametocytes*, develop The latter remain for long periods in the blood-stream and undergo no further development unless ingested by the mosquito

In vivax ovale and possibly malariae and ovale infections it is believed that a liver or *exo-erythrocytic* (*E E*) phase of the parasite occurs, probably originating from the pre-erythrocytic phase Relapses of these forms of malaria depend on the persistence of these exo-erythrocytic parasites which from time to time eject infective merozoites into the blood-stream and so re-establish the erythrocytic (E) cycle. In falciparum malaria exo-erythrocytic forms do not develop and that the pre-erythrocytic forms do not persist Hence recrudescences result from the multiplication of existing blood (E) parasites, and true relapses do not occur

ENDEMICITY

Malaria in a community may be either stable or unstable Stable malaria occurs in regions in which there is constantly repeated infection Malaria in such areas is called 'holoendemic' The population has a high degree of immunity and epidemics do not occur Unstable malaria occurs in regions in which transmission is intermittent, for example, where it is seasonal or in populations inadequately protected by drug suppression or entomological control In such areas the population has a varying degree of immunity and epidemics are liable to occur

ACQUIRED RESISTANCE TO MALARIA

The severity and duration of malaria attacks depend on many factors, including the nutritional status of the host and the virulence of the infecting strain The most important modifying factor, however, is the development of resistance or immunity in the infected individual

Certain individuals are naturally more resistant than others to malarial infection They may live continously for years in endemic areas without developing a clinical attack, or may fail to become infected after artificial inoculation with parasites Most subjects, however, are readily susceptible to infection, and continuous reinfection or

obtain (i) the presence of suitable anopheline mosquitoes, (ii) a reservoir of malaria infection (usually the local population), (iii) suitable non-immune or partly immune hosts, and (iv) an environmental temperature of between 65° and 85° F with suitable humidity. It does not as a rule occur in regions higher than 6000 feet above sea level

THE CAUSATIVE ORGANISM

Human malaria may be caused by the following plasmodia. Mixed infections occur:

P. vivax (benign tertian malaria or vivax malaria).
P falciparum (malignant tertian, subtertian or falciparum malaria)
P malariae (quartan malaria or malariae malaria).
P ovale (ovale tertian malaria or ovale malaria).

Of these infections the commonest and most important are those caused by *P. vivax* and *P falciparum.*

LIFE CYCLE

The life cycle of the parasite is essentially the same in all species of plasmodia.

(a) *The Life Cycle in the Mosquito* (Sporogony)

[illegible]

female cell or gamete developed from an ingested female gametocyte The fertilized cell penetrates the stomach wall and develops beneath the lining membrane, eventually becoming a large cyst within which appear the infective forms of the parasite, called sporozoites. After 7-20 days, depending upon the external conditions, the cysts rupture and the sporozoites migrate, many reaching the salivary glands The infected mosquito injects sporozoites into the host's tissues during a blood meal

(b) *The Life Cycle in Man* (Schizogony)

Sporozoites rapidly disappear from the blood-stream after infection During the succeeding 5 to 7 days the parasite develops further in the polygonal cells of the liver and possibly elsewhere (the so-called *pre-erythrocytic (or P E) cycle*) At the end of this period (called the *prepatent* period) merozites are thrown into the circulation and invade erythrocytes, starting the *asexual life cycle (Erythrocytic or E cycle)* which is repeated at regular intervals In the erythrocytes the youngest forms appear as unpigmented discs or rings of cytoplasm containing one or more small masses of chromatin As the parasite grows it becomes actively amoeboid and develops granules of brown pigment called

The anaemia causes some degree of anoxaemia, which is associated with local tissue anoxia of varying severity The latter is of fundamental importance in the genesis of pathological tissue changes

[illegible]

circulation are the physiological responses to high fever, and the profound effects of medical shock (vascular failure) Local circulatory phenomena include the development of stasis in the brain, the reduction and redistribution of the renal circulation in the condition of renal anoxia, and changes in the liver blood flow which lead to centrilobular congestion and degeneration

Mechanical interference with local circulation may also be caused by changes in the blood cells, such as the development of 'stickiness' in relation to phagocytes and the vascular endothelium, or the 'sludging' of erythrocytes, and by the swollen and often overladen phagocytic cells such as the Kupffer cells of the liver

Malarial pigment is derived from haemoglobin It is particulate, insoluble and not itself toxic The general pathological pattern is, however, influenced by its appearance in the tissue spaces and phagocytic cells

The processes outlined above are concerned in the evolution of the pathological changes often seen at necropsy, e g the early stasis and subsequent haemorrhage and thrombosis in and about the small vessels of the brain, the centrilobular degeneration and necrosis of liver cells, the renal anoxia kidney with ischaemic cortex and congested stased medullary vessels, and the diffuse brown or black pigmentation of the liver, spleen or bone marrow

Details of the lesions are unnecessary here It is essential for the physician, however, to understand that many of the pathological processes concerned in malaria are reversible and prompt treatment may prevent or modify their development

CLINICAL PATHOLOGY

Alteration in erythrocyte counts and haemoglobin concentrations occur in proportion to the degree of erythrocyte destruction and hae-

[illegible]

volume may cause haemoconcentration with artificially high counts and haemoglobin concentrations

The thin blood film may show considerable variation in erythrocytic size, including some macrocytosis There may be poikilocytosis and

long continued infection over many years usually leads to the establishment of some degree of acquired resistance, especially to superinfection (i e infection with the same strain of parasite). Some authors believe that immunity in human malaria is dependent, as in bird malaria, upon the persistence of a latent blood infection in the host. There is, however, ample evidence that humoral immune bodies are developed during a malarial attack, and it has been found that immunity may occasionally persist for some time after the termination of the infection.

The immunity takes time to build up, so that as a rule non-immune individuals suffer most severely from malaria in their early years of exposure

In the indigenous population of a malarious area the active disease is usually rare in very young infants but is extremely common and often severe in the latter half of the first year of life As the child grows older the attacks get milder, and, provided there is continued reinfection by the same strain of parasite, the overt disease eventually becomes very much modified and ameliorated in the older child and the adult.

Where infection is interrupted for any considerable length of time the acquired powers of resistance rapidly decline and the individual becomes open to severe attacks on reinfection In communities such diminution of resistance is the forerunner of epidemics

PATHOLOGY

For the first 5 to 7 days after injection into the human host, sporozoites develop in the epithelial cells of the liver (the pre-erythrocytic phase) The immediate pathological significance of this phase, beyond the destruction of a few liver cells, is unknown

The invasion of the erythrocytes which follows the maturation of the tissue phase and the liberation of merozoites into the blood is the basic pathological process in clinical malaria

The powers of invasion of the species of plasmodia differ considerably. *P vivax* develops most easily in the youngest erythrocytes, so that at any one time not more than 2 per cent of erythrocytes are invaded *P malariae* develops chiefly in the older red cells, the infection rate seldom exceeding 1 per cent *P falciparum* invades all ages of erythrocytes indiscriminately so that very high infection rates may occur.

With each sporulation, the invaded red cells are destroyed Furthermore, varying numbers of uninvaded red cells are lysed during the attack, and both parasitized and unparasitized cells are phagocytosed in large numbers by the cells of the spleen and liver Anaemia thus usually develops, the severity of which depends as a rule on the species of invading plasmodia Anaemia is most pronounced in falciparum infections, where the loss of red cells may be very extensive and rapid.

larly if haemoglobin is also present Hyaline and granular casts are common and may be present in large numbers together with erythrocytes in cases in which acute renal dysfunction develops

CLINICAL FEATURES

INCUBATION PERIOD

The time elapsing between the inoculation of sporozoites in man, i e the infective bite, and the appearance of clinical signs is referred to as the *intrinsic incubation period* The length of this period varies with the plasmodial species involved It is usually 10 to 15 days, but may be some weeks or months

The time elapsing between the ingestion of infected blood by the mosquito and the appearance of sporozoites in the salivary glands, i e the period required before the insect becomes infective to man, is known as the *extrinsic incubation period*

PERIODICITY

The periodic elevations of temperature and associated phenomena, i e the *paroxysms,* occurring in the classical malarial attacks are roughly contemporaneous with the sporulation of the parasite The interval at which they recur is known as the periodicity of the infection When the cycle of schizogony is so adjusted that sporulation occurs at 48 hours, so that the paroxysm occurs every third day, and the periodicity is tertian The periodicity of paroxysms in falciparum malaria frequently indicates a parasite life cycle of 36 rather than 48 hours, paroxysms in such infections occur at intervals of less than 48 hours and the fever peaks consequently occur slightly more frequently than every third day, giving rise to the so-called subintrant fever (hence the term subtertian malaria) In *P malariae* infections the erythrocytic cycle takes 72 hours Fever peaks occur every fourth day, and the periodicity is thus quartan In all infections, sporulation may occur daily, with daily paroxysms (quotidian periodicity)

THE ATTACK

Primary Attack The attack immediately succeeding the intrinsic incubation period is known as the primary attack

Relapse A relapse is a recurrence of the clinical signs and symptoms of malaria and the reappearance of parasites in the peripheral blood following a period of quiescence after the subsidence of the primary attack *True relapses* arise in vivax, ovale and malariae infections as the

punctate basophilia. There may occasionally be a high reticulocyte count, but this does not commonly occur until some days after the start of specific therapy In severely anaemic cases nucleated red cells may be present. These are nearly always normoblastic in type; megaloblasts are very rare.

The colour index is one or less, very seldom greater than one, except in cases complicated by malnutrition.

The bone marrow response is essentially normoblastic. There is often considerable erythroblastic activity without corresponding reticulocytosis in the peripheral blood.

The chemical make-up of the blood depends on factors such as the state of the liver and kidney function and the water-electrolyte balance of the body *There are no chemical findings specific to malaria In some* cases there may be raised plasma potassium, especially during severe lysis Sodium and chloride concentrations are frequently low, especially where there is severe vomiting or diarrhoea.

In severe lysis there may be haemoglobin and methaemalbumin in the plasma

The total plasma protein concentration may be unaltered or low. The albumin/globulin ratio may change, due to decrease in the former and increase in the latter, usually in the gamma globulin fraction. Certain serum tests of doubtful value for diagnosis or prognosis of malaria depend on these changes in blood protein.

Cases in which hepatic dysfunction is evident show an increase in bilirubin in the plasma and sometimes in the urine The van den Bergh reaction is indirect, direct or biphasic, depending on the degree of liver damage and the rate of haemolysis Hepatic function tests usually show

of acute uraemia.

The urine should always be examined in malaria. The volume passed is important.

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result of fresh infection of erythrocytes by merozoites derived from active persistent liver forms (EE forms) of the parasites. They often occur at regular intervals and are usually shorter in duration and milder than the primary attack The periodicity is usually similar to that of the primary attack.

An attack of malaria should be considered as a relapse only when the possibility of reinfection can be excluded.

Recrudescences In *P falciparum* infections, in the absence of persistent EE forms, true relapses do not occur Recrudescence of the clinical attack results from the continued existence of the original erythrocytic (E) cycle in the blood

Reinfection A reinfection is a fresh infection in an individual who has previously had malaria Reinfections with the same strain follow much the same clinical course as the primary attack except when the host has developed acquired resistance. In the latter case the clinical course is much milder than in the primary attack

VIVAX MALARIA:[1] BENIGN TERTIAN MALARIA

INCUBATION PERIOD AND PRODROMAL SYMPTOMS

The intrinsic incubation period is usually 10 to 15 days. In a few strains it may be some months The appearance of the primary attack is often considerably delayed in individuals who had been receiving suppressive chemotherapy during exposure In such individuals, the first clinical attack may not appear until some months after the drug dosage has been stopped

In the last two or three days of the incubation period prodromal symptoms are common The patient frequently complains of headache, limb pains, backache, anorexia and sometimes nausea and vomiting There may be mild shivering attacks during which the patient complains of feeling cold In relapses prodromal symptoms are often absent

THE CLASSICAL ATTACK

Onset. In the primary attack the onset may be associated with a rigor but this is unusual For the first few days the fever is irregularly remittent or intermittent During this period rigors are uncommon The pattern of *intermittent regularly recurring febrile paroxysms* is usually established by the end of the first week

The Paroxysm. For some reason paroxysms occur as a rule more frequently in the afternoon and evening than in the morning. The

[1] Ovale malaria is very similar to vivax malaria and is not described here.

fully-developed paroxysms may be divided into three clinical stages,

shiver and finally passes into rigor The temperature at the start of

TERTIAN FEVER
P VIVAX INFECTION

FIG 29 Tertian fever in *P vivax* infection
[From B G Maegraith, *Pathological Processes in Malaria and Blackwater Fever*, Blackwell Scientific Publications, Oxford, 1948]

often raised Nausea and vomiting are common and may be severe enough to suggest food poisoning Frequency and polyuria are usual

The hot stage succeeds the cold The rigor ceases, the subjective feeling of cold disappears and the patient complains of being uncomfortably

hot The temperature frequently remains at about the level reached at the end of the cold stage, but occasionally may rise, and in rare circumstances may continue to hyperpyrexial levels The pale skin now flushes and feels hot and dry The blood-pressure tends to fall; the pulse is full and bounding Respiration is rapid, nausea and vomiting are common, and the patient frequently complains of severe thirst. At this stage he becomes restless and excitable, and may go into delirium One of the most severe subjective complaints is that of post-orbital headache

The hot stage lasts longer than the cold, frequently two hours or more, but eventually it passes into the third or *sweating stage*. Sweating first appears at the temples, and rapidly becomes generalized and copious. The temperature falls to normal or subnormal in the course of an hour or so. The pulse rate becomes normal and with the subsidence of the temperature the patient usually passes into an exhausted sleep from which he awakes considerably refreshed.

The Interval· The period between the subsidence of fever and the appearance of the next paroxysm is known as the interval In the interval the patient feels well and the temperature is within normal limits in the majority of cases, although it may occasionally rise to 100° or 101° F

Erythrocytes· Parasitized red cells are destroyed at sporulation and many unparasitized cells may also be lysed. Some degree of anaemia therefore develops This is not often severe in vivax malaria, although it may occasionally reach serious proportions in children The blood picture may show some macrocytosis and poikilocytosis, anisocytosis, and chromatophilia, and may thus superficially resemble that of pernicious anaemia. The colour index, however, is usually about 1.0, and the bone-marrow reaction is normoblastic and not megaloblastic There may be a slight increase in reticulocytes during the early stages of the paroxysms, but these cells do not increase in numbers as a rule until after administration of specific drug therapy.

Leucocytes. There is often a mild leucopenia.

Parasites in the peripheral blood. Representatives of all forms of the asexual parasite from the early ring to the mature schizont may be recognized in the peripheral blood at any one time, though one particular stage greatly preponderates at certain stages once regular periodicity is established Gametocytes are usually present after the infection has been going on a week or more. The number of invaded erythrocytes is seldom over 2 per cent of the total cells

Spleen· The spleen is often sufficiently enlarged to be palpable by the end of the second week of the attack. It may sometimes be felt to increase in size during the paroxysm

Herpes Labialis· This is present in about one-third of all cases It

frequently precedes the malarial attack and disappears rapidly after antimalarial treatment has commenced

In very severe cases, renal and hepatic complications may appear. These are, however, very much more common in falciparum malaria and will be discussed later.

COURSE AND PROGNOSIS

In untreated primary infections paroxysms recur regularly for six weeks to three months or more, depending upon the strain of parasite, before spontaneous clinical cure occurs Spontaneous cure is frequently heralded by the lengthening of the intervals between paroxysms, and by reduction in their severity both in regard to the appearance of rigors and the temperature reached

Relapse Relapses occur after a period of clinical quiescence which may last for some weeks or months. The clinical features of a relapse are similar to those of the first attack, except that the initial period of irregular fever is absent The onset is accompanied by rigor and paroxysm, and periodicity similar to that of the parent attack is established from the start The relapse is commonly less severe and of shorter duration than the first attack It is unusual in vivax malaria for relapse to occur more than three years after the patient has left the endemic area

MALARIAE MALARIA QUARTAN MALARIA

INCUBATION PERIOD AND PRODROMAL SYMPTOMS

The incubation period is frequently longer than that of vivax malaria It may be as long as 30 to 40 days and in some cases even several months Prodromal symptoms similar to those of vivax malaria develop in the last few days of the incubation period Parasites may be observed in the blood before symptoms develop

THE ATTACK

Onset The onset of the disease is often insidious The clinical picture may be more severe than that of vivax malaria The primary attack frequently starts with a paroxysm, followed by regular periodicity, which is quartan in type when the majority of broods of the parasite undergo schizogony together All variations from quartan to quotidian periodicity may occur, but quartan is the commonest In this form of malaria, the periodicity may vary from time to time in the same individual during the same attack

The Paroxysms and Interval. The three stages of the paroxysms are clearly distinguished Rigors may occasionally be absent, on the whole they are commonest in attacks in which the periodicity is quartan

Sometimes the cold stage is prolonged The hot stage frequently lasts several hours Nausea and vomiting are extremely common during this stage. The sweating stage is often followed by a fall of temperature

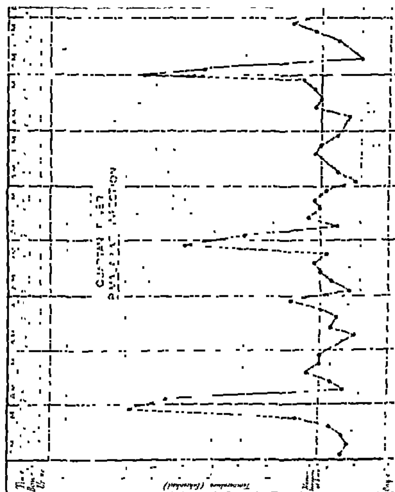


Fig 30 Quartan fever in *P malariae* infection
[From B G Maegraith, *Pathological Processes in Malaria and Blackwater Fever*, Blackwell Scientific Publications, Oxford, 1948]

to well below normal and may end in the partial collapse of the patient.

Erythrocytes: The anaemia is usually less pronounced than in vivax malaria, but may occasionally be severe It is normocytic, with a colour index of 1·0 or less.

Leucocytes There is usually some leucopenia

Parasites in the Peripheral Blood Representatives of all stages of the asexual parasites are usually present at any one time, the dominant form depending on the periodicity. As a rule less than 1 per cent of red cells are infected Gametocytes appear within a few weeks of the onset of clinical signs.

The Spleen The spleen is not usually enlarged to the same extent as in the other infections It is, however, commonly palpable within a fortnight from the onset.

Herpes Labialis is common

Oedema, especially of the ankles, is not uncommon in the acute attack

COURSE AND PROGNOSIS

The acute attack of quartan malaria is self-limited It may last for several months before spontaneous clinical cure The disease is rarely fatal and seldom gives rise to pernicious complications Quartan malaria is the most persistent form of human malaria Relapses are common, and may occur many years after the primary attack After long continued or recurrent infections a syndrome closely resembling hydraemic nephrosis may develop, especially in children

FALCIPARUM MALARIA MALIGNANT TERTIAN MALARIA (SUBTERTIAN)

This is the most serious form of malaria Attacks may be uncomplicated or associated with serious and often fatal complications

INCUBATION AND PRODROMAL SYMPTOMS

The incubation period varies from 8 to 15 days Prodromal symptoms, which are often severe, occur during the last few days of the incubation period The patient is depressed and unwell He complains of severe headache, bone and muscle pains, especially nagging backache in the lumbar or sacro-iliac region Shivering feelings, nausea and vomiting or diarrhoea are frequent

THE UNCOMPLICATED ATTACK

Onset Parasites may exist in the blood for long periods before the onset of severe symptoms, especially in individuals who have built up some acquired resistance or who are misusing suppressive drugs In such cases the onset is insidious, with symptoms such as diarrhoea, persistent dyspepsia, malaise and backache which may not at first suggest malaria.

Sometimes the cold stage is prolonged. The hot stage frequently lasts several hours Nausea and vomiting are extremely common during this stage The sweating stage is often followed by a fall of temperature

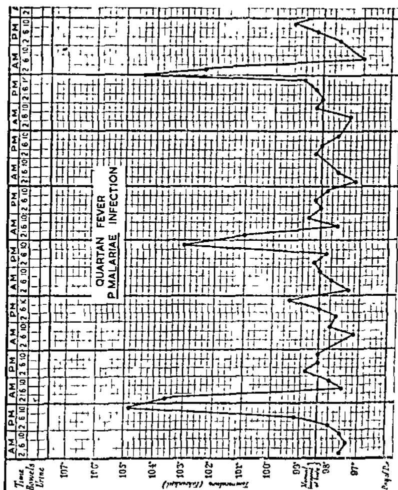


Fig 30 Quartan fever in *P malariae* infection
[From B G Maegraith, *Pathological Processes in Malaria and Blackwater Fever*, Blackwell Scientific Publications, Oxford, 1948]

to well below normal and may end in the partial collapse of the patient

Erythrocytes The anaemia is usually less pronounced than in vivax malaria, but may occasionally be severe It is normocytic, with a colour index of 1 0 or less.

little red cell destruction The red cell count and haemoglobin concentration may be temporarily much increased by the appearance of shock and the associated sudden loss of circulating blood volume.

The anaemia is normocytic and the colour index is 1 0 or less.

The bone marrow reaction is normoblastic

Leucocytes There is usually a leucopenia with a count of the order of 3000 to 6000 cells per cu mm Granulocytes are reduced and there is an increase in large mononuclear cells. In severe cases haemozoin pigment may be present in circulating polymorphs and monocytes

Parasites in the peripheral blood In this infection the later stages of schizogony probably take place in tissue vessels so that normally only the younger growing forms (rings) of the parasites appear in the peripheral blood In heavy infections all forms may be present Very high rates of infection of erythrocytes (for example, 20 or 30 per cent) may occur Gametocytes appear within a few days of the onset of the primary clinical attack and may persist for months after cure

In the untreated case the parasitaemia increases as the disease progresses, but there may be appreciable daily variations in the parasite density, which demand repeated examination of the peripheral blood at intervals of a few hours

Pulse The pulse rate is usually fast but in patients with low grade fever or in individuals who have some acquired resistance to the infection bradycardia may develop and persist into convalescence

Abdominal Symptoms Nausea and vomiting are common from the onset and may be very severe Epigastric discomfort, anorexia and dyspepsia are common Watery diarrhoea is frequent and is particularly notable in infections with certain strains of the parasite, especially those prevalent in West Africa

The Spleen The spleen enlarges rapidly in all cases, and is usually palpable within 10 days of the onset Its size sometimes increases during paroxysms, decreasing again in the interval The enlarged organ is usually tender and there may be tenderness in the splenic region even when the organ is not palpable After repeated attacks, especially in children, the spleen may become enormous In frequently reinfected adults it is sometimes fibrotic and may be smaller than normal

Sudden splenic infarction and perisplenitis may cause acute tenderness over the splenic area in the left hypochondrium or pain in the left shoulder region Surgical emergencies may arise from sudden rupture of the spleen or torsion of its pedicle

The Liver. Deviations of 'function' tests and enlargement of the liver probably occur in all cases In some, especially where gastrointestinal symptoms are evident, the liver may be tender and palpable beneath the costal margin Jaundice appears in severe cases

The onset of the overt attack is, however, usually well defined Shivering feelings and chills are common, but there is usually no well defined rigor.

The Attack: The patient usually presents with obvious fever, flushed dry skin and bright eyes. He looks like a case of moderately severe influenza and may not appear very ill. This appearance is deceptive, however, since serious complications may arise at any stage of either a primary attack or a relapse.

The headache, bone and muscle pains and malaise of the prodromal period persist and increase as the attack develops.

Anxiety, mental confusion and delirium are common. The patient *is more asthenic and prostrated than in vivax infections and in those* cases in which periodic fever becomes established, the feeling of well-being which normally accompanies the interval between the paroxysms in vivax malaria is absent.

Fever. The fever is usually irregular at first, and shows no sign of periodicity. In about a third of cases periodicity becomes evident after the first few days and is commonly subtertian or quotidian The paroxysms are often not as regular as in vivax infections and the temperature peaks tend to occur at about 36-hour periods (subtertian). The temperature during the intervals may not fall to normal The hot stage is frequently prolonged so that the fever becomes remittent, intermittent or continuous. Sometimes there are double peaks of high fever resembling those occasionally seen in kala azar Even in severe attacks the fever may not be high. It may be absent until towards the end of the attack or until the appearance of complications Occasionally there may be no fever at any stage, even in the presence of heavy blood infection.

Sweating Sweating is common but there is usually no well-defined sweating phase, it is often persistent in cases where the fever is low Where the fever is periodic there is a sweating phase as in vivax malaria In cases in which the temperature is high sweating may be absent.

Erythrocytes Because of the invasive properties of the parasites and the ease with which unparasitized erythrocytes are lysed, severe anaemia is common in falciparum malaria Red cell counts of fewer than a million cells per cu mm with a corresponding fall in haemoglobin concentration may be recorded. In cases of average severity the red *cell count varies from 2 5 to 3 0 million cells per cu mm, in mild cases* there may be little or no obvious anaemia In severe cases the loss of *red cells may be so rapid that haemoglobin is liberated into the plasma* and passed in the urine, giving rise to the syndrome of blackwater fever.

The degree of anaemia is not always an indication of the severity of the attack; fatal complications sometimes occur in cases with apparently

are (1) cerebral malaria, (2) hyperpyrexia, (3) gastrointestinal malaria, and (4) algid malaria Blackwater fever is usually regarded as a complication of malaria. This syndrome is described separately

(1) CEREBRAL MALARIA

This syndrome commonly unfolds over a period of days It may, however, appear suddenly with the rapid development of coma The patient complains of headache and frequently of drowsiness If untreated, he passes into coma with the pupils contracted (often unequally) and deep reflexes abolished or exaggerated All kinds of neurological signs may be present, the Babinski sign may be positive, hemiplegia may develop, there may be stiffness of the neck, or muscular twitching and convulsions resembling those of epilepsy Acute mental disturbances are common, in endemic areas such disturbances should be considered malarial in origin until proved otherwise The clinical picture is frequently a mixed one from the point of view of the nervous system, but forms of cerebral malaria are sometimes referred to as epileptiform, cataleptic, meningeal, paretic and so forth, depending on the prevailing nervous signs There is usually irregular remittent fever and often severe anaemia Parasites, including schizonts, are usually present in large numbers in the peripheral blood

(2) MALARIA HYPERPYREXIA

Hyperpyrexia may develop immediately or during the course of an apparently mild attack It sometimes occurs in association with cerebral malaria The skin is hot and dry and there may be some cyanosis in the extremities It is important to note the dryness of the skin, which indicates inhibition of sweating By the time the patient is seen he is usually *in delirium In untreated cases coma supervenes, accompanied by in*continence of urine and faeces

Malarial hyperpyrexia may be clinically indistinguishable from heat hyperpyrexia It is thus always essential in an endemic area to exclude malaria before a diagnosis of heatstroke can be safely made

The peripheral blood is usually heavily infected, schizonts as well as ring forms are commonly present

(3) GASTROINTESTINAL SYNDROMES

(a) *Bilious remittent fever* This syndrome varies considerably in

Respiratory Symptoms: The respiration rate in falciparum malaria is usually increased and in infection with some strains, notably those found in the Balkans and West Africa, there is often some involvement of the lungs producing signs and symptoms varying from cough associated with a few scattered moist sounds to signs of bronchopneumonia or frank pulmonary oedema.

Renal Symptoms: Indication of renal disturbances may occur in falciparum malaria. There is often albumin present in the urine and granular and hyaline casts are common. The concentration of urinary chloride is often low, even in the absence of dehydration, indicating some tubular dysfunction

More severe renal involvement occasionally develops, with oliguria, sometimes proceeding to anuria, and associated uraemic symptoms A syndrome similar to acute nephritis with oliguria and the passage of urine containing albumin, blood cells and casts may also occur

Herpes labialis is present in about one third of cases.

COURSE AND PROGNOSIS

If the acute attack is adequately treated and no pernicious symptoms develop there is little risk to life.The acute attack is usually of shorter duration than that of either vivax or malariae malaria. Recrudescences are not uncommon They do not usually appear later than 9 to 12 months after the initial attack but have been reported as long as two years after Severe anaemia and splenomegaly develop in patients constantly exposed to reinfection or to a series of acute attacks The frequently infected patient may pass into the state of malarial cachexia, the clinical picture of which is often complicated by malnutrition. This condition in children may be fatal.

PERNICIOUS MALARIA

Pernicious complications may develop without warning at any stage in falciparum malaria Complications appear most commonly in individuals who have suffered repeated attacks especially when these have been inadequately treated

Pernicious symptoms may be anticipated if more than 5 per cent of

is apparently light; an appreciable infection rate may sometimes be present in immunes without clinical signs

The syndromes of pernicious malaria are usually grouped according to the organs which are principally involved The commonest forms

MALARIA IN CHILDREN

In tropical countries malaria is one of the great causes of morbidity and mortality in children The clinical attack is rare in the first months of life, but thereafter babies are especially prone to pernicious forms of malaria and even vivax and malariae malaria may occasionally be fatal to them, particularly if they are suffering from comcomitant malnutrition Rupture of an enlarged spleen following external violence is a serious risk in falciparum and vivax infections

The clinical picture of malaria in children depends on whether they are suffering from acute recent infection, or from the effects of frequent reinfection or long-continued infection or both

The acute form is often totally different from the adult disease It is seen most commonly in children who have not had the full benefit of protective measures, or who live in areas where malaria is seasonal

The infected child is dull, restless and miserable with no appetite. It resents feeding and food is often vomited back Bile may be present in the vomit There is frequently severe abdominal colicky pain, considerable wind and diarrhoea, the stool sometimes containing bile The abdomen is distended and tender, especially in the hepatic and splenic areas The spleen is usually palpable and commonly the liver also As the re[illegible]

ranges from 101° to 105° F and the fever may be continuous, remittent or intermittent Rigors are uncommon Convulsions are common, there may be meningismus

If the condition is allowed to continue for long, the anaemia becomes more severe, the abdomen more distended, the spleen (and often the liver) larger, and there is often rapid loss of weight and wasting of the limbs sometimes associated with puffiness of the face

If the malaria remains untreated the child may become rapidly worse and die, or it may temporarily recover with the abatement of most or all of the signs and symptoms and gradually slip into the progressive ill-health and recurrent fever of so-called 'chronic' malaria

This form of malaria is commonest in falciparum areas and is seen in children of all ages up to adolescence The normal growth of the child is retarded The patient is listless, wasted, with thin skinny flaccid limbs and a huge protuberant abdomen There is chronic

watery and contains both blood and bile. The liver becomes enlarged and tender from about the second day, and icterus appears on the first or second day, becoming progressively more severe. The direct van den Bergh reaction is positive The urine volume is scanty and the urine contains granular and hyaline casts, albumin and bilirubin. Renal failure may supervene with the development of anuria and acute uraemia Death occurs in severe cases from vascular collapse or acute hepatic failure. Parasites including schizonts are present in large numbers in the peripheral blood.

(b) *Dysenteric malaria*: This may be clinically indistinguishable from acute bacillary dysentery. It is characterized by the passage at frequent intervals of stools containing blood, mucus, epithelial and other cellular debris, and, in some cases, pus cells. The abdomen is tender and retracted. Nausea and vomiting are common and the temperature is usually high and remittent There is nearly always heavy parasitaemia

(c) *Choleraic malaria*: The patient suffers from profuse watery diarrhoea, nausea and vomiting, muscular cramps in the limbs and abdomen, and progressive dehydration. The stool is mainly fluid, containing particles of faeces and small quantities of blood and mucus The salt content of both blood and urine is low Medical shock and suppression of urine may occur, as in cholera. Parasites are usually present in the blood in large numbers.

(4) ALGID MALARIA

In this condition the patient passes rapidly into medical shock, frequently associated with coma. The facies are drawn, and pinched, the eyes sunken The skin is inelastic, pale and covered with clammy sweat. Although the skin feels cold the rectal temperature may be raised to 101° to 102° F. The breathing is shallow and sighing The pulse is thin and fast; both systolic and diastolic blood pressures are low, the diastolic being frequently unmeasurable There is often acute reduction in circulating blood volume, evidenced by haemoconcentration.

There may be intense epigastric discomfort, persistent vomiting, and sometimes choleraic diarrhoea Parasites, including schizonts, are commonly present in very large numbers in the peripheral blood. Algid malaria often develops during an apparently mild attack of falciparum malaria Its onset is independent of the prevailing degree of parasitaemia or anaemia

The untreated condition is fatal, the patient dying from vascular failure. The clinical picture in some ways resembles that of acute adrenal insufficiency.

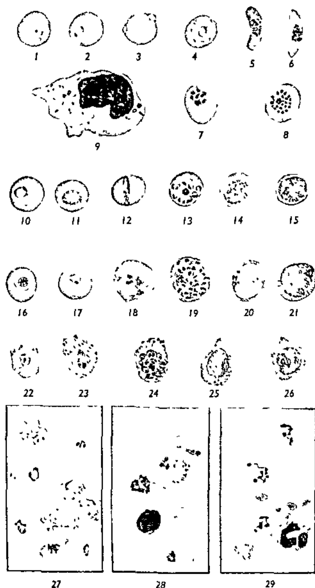


FIG 31 Malaria parasites in thin and in thick blood films

The spleen is very large and may present into the pelvis The liver is frequently enlarged and tender Rupture of the enlarged spleen may follow external violence.

The condition if untreated becomes progressively worse and passes into the state of malarial cachexia, which ends fatally.

MALARIA IN 'IMMUNES'

In individuals who have acquired some resistence to local plasmodial strains the clinical effects of malaria resulting from infection with these strains are greatly modified. Irregularly spaced febrile attacks of short duration occur, which do not usually resemble ordinary malaria. There is malaise, headache, often backache, anorexia and sweating. The response to treatment is rapid (see p 219). More severe attacks develop as immunity is weakened or lost, for instance as a result of the irregular or careless use of antimalarial drugs or incomplete entomological protection. Blackwater fever may follow re-infection with *P. falciparum* in the latter circumstances

MALARIA IN PREGNANCY

Malaria is a common cause of premature labour and abortion, especially in the last months of gestation The mother may die from malaria following childbirth if the disease is untreated In hyperendemic areas pregnant women not infrequently come to term with severe anaemia, enlarged spleens sometimes presenting into the pelvis, and enlarged livers In such women mechanical factors may lead to elevation of the diaphragm and difficult delivery. The anaemia will respond to antimalarial therapy

uterus Post-partum rises of temperature are often caused by malaria Children born of infected mothers are often marasmic and difficult to rear. Malaria may be transmitted occasionally from mother to child across the placenta. It is believed that this occurs as the result of some intra-uterine placental accident.

FC
QT2
FG1
VS
QT2
QT1
P
QT2
FG1
QT1
QT2
VT
P
QT1
QT2
FG2
L
QT2
VS
VT2
L
FC
P
VT2
FT
VG
E
VT1
FT

KEY

FIG 32 Thick films made with equal quantity of an avian red cell suspension of known cell concentration to facilitate parasite counting

Key to Fig 32 FC, avian erythrocytes P, polymorph L, lymphocyte E, eosinophil FT, *falciparum* early trophozoites, distinctive size and numbers, FG_1, *falciparum* characteristic gametocyte FG_2, contracted *falciparum* gametocyte resembling late trophozoite or gametocyte of malaria VT_1, *vivax* early trophozoites, not distinctive VT-VT_2, late *vivax* trophozoites with characteristic cytoplasmic scatter VS, typical *vivax* segmenter VG, *vivax* gametocyte with characteristic size, shape and undivided chromatin QT_1, early malaria trophozoite, not distinctive QT_2, late *malariae* trophozoite with distinctive small, compact form

[From P F Russell, *Malaria*, Blackwell Scientific Publications, Oxford 1952, after J W Field]

Method Solutions A and B are made up and placed in wide-mouthed jars A third jar contains water for washing, which should be frequently renewed

Dip the slide in solution A for 1 second

Wash by waving gently for a few seconds in water

Shake

Dip in solution B for 1 to 3 seconds

Wash as before

Dry slides in vertical position

Result Lysis with loss of haemoglobin occurs during staining In the final preparation the parasites are stained (cytoplasm blue, chromatin reddish blue) and the erythrocytes are not White cell nuclei and platelets stain blue and pinkish respectively

Jars of stain left on benches sometimes become invaded by bacteria which can be filtered off quite effectively by ordinary filter paper

Differentiation of species depends on factors outlined in Figures 31 and 32 and Tables III and IV

All forms of the asexual parasite are to be found in the peripheral blood in cases of vivax, malariae and ovale malaria Only ring forms are as a rule found in the peripheral blood in falciparum malaria unless the rate of infection of red cells is very high, when growing forms and schizonts appear

In all infections sexual forms may be present after the first few days of illness

The blood should be examined frequently during an attack This is particularly necessary in falciparum malaria in which the numbers [illegible]

[illegible]

good clinical grounds otherwise, be taken off drugs until the diagnosis is confirmed

CLINICAL EVIDENCE

Malaria must be suspected in all cases of fever in endemic areas until proved otherwise Clinically the regular succession of paroxysms and fever-free intervals will usually make the physician suspect the presence of malaria The combination of anaemia and enlarged spleen is highly suspicious in an endemic area The co-existence of *herpes labialis* is strongly presumptive evidence Malaria may often clinically resemble other conditions For instance, it may evoke a set of symptoms very similar to those of acute surgical abdominal conditions, such as

THE DIAGNOSIS OF MALARIA

The certain diagnosis of active malaria depends upon the identification of the parasites in the peripheral blood or elsewhere (e g. the sternal marrow). Where the parasites are difficult to find in the blood, examination of the marrow is unlikely to help the diagnosis.

The presence in the blood of trophozoites or later growing forms, indicating the progress of an active asexual cycle, must be established.

The discovery of gametocytes only is not sufficient to confirm the diagnosis of active malaria Gametocytes are not usually formed until schizogony has been proceeding for some days. They may frequently be found in the peripheral blood weeks and even months after the overt attack has subsided or been cured

Blood-films For the diagnosis of the presence of parasites the examination of stained thick blood-films is sufficient. The species of plasmodium present can be usually detected in the thick film and confirmed by examination of a thin film, prepared in the ordinary way and stained by Leishman's method

The thick film Clean the tip of a finger or lobe of an ear with alcohol and allow to dry Prick with a cutting needle and squeeze gently until a large globule of blood exudes Pick up the blood with the under surface of a clean glass slide Spread it evenly over a circular area of the surface about ⅜" across with the needle or corner of another slide.

Allow the film to dry thoroughly before staining

Field's stain is recommended for general use.[1]

FIELD'S STAIN

Solution A

Methylene blue (medicinal)	0 8 gm
Azure I	0 5 gm
Disodium hydrogen phosphate (anhydrous)	5 0 gm
Potassium dihydrogen phosphate	6 25 gm
Distilled water	500 0 cc

Solution B

Eosin	1 0 gm
Disodium hydrogen phosphate (anhydrous)	5 0 gm
Potassium dihydrogen phosphate	6 25 gm
Distilled water	500 0 cc

[1] J S B stain may be used as an alternative and has the advantage of being serviceable for both thick and thin films which have been preserved for some time. See P F Russell, *Malaria*, Blackwell Scientific Publications, Oxford, 1952

Giemsa staining method for thick films: add 10 ml. Giemsa stain to 100 ml. phosphate buffer solution. Immerse thick films Leave for twenty minutes. Remove slides and wash gently in tap water. Drain and dry

Method Solutions A and B are made up and placed in wide-mouthed jars A third jar contains water for washing, which should be frequently renewed

Dip the slide in solution A for 1 second

Wash by waving gently for a few seconds in water

Shake

Dip in solution B for 1 to 3 seconds

Wash as before

Dry slides in vertical position

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In all infections sexual forms may be present after the first few days of illness

The blood should be examined frequently during an attack This is particularly necessary in falciparum malaria in which the numbers of parasites present may vary considerably during the day Failure to find parasites in one examination is not significant Repeated examination of films made morning and evening over periods of days may be necessary, particularly if the patient has been taking suppressive antimalarial drugs In the latter case the patient should, unless there are good clinical grounds otherwise, be taken off drugs until the diagnosis is confirmed

CLINICAL EVIDENCE

Malaria must be suspected in all cases of fever in endemic areas until proved otherwise Clinically the regular succession of paroxysms and fever-free intervals will usually make the physician suspect the presence of malaria The combination of anaemia and enlarged spleen is highly suspicious in an endemic area The co-existence of *herpes labialis* is strongly presumptive evidence Malaria may often clinically resemble other conditions For instance, it may evoke a set of symptoms very similar to those of acute surgical abdominal conditions, such as

TABLE III

DIFFERENTIATION OF HUMAN MALARIA PARASITES

	P vivax	*P falciparum*	*P. malariae*	*P ovale*
Duration of schizogonous cycle	48 hours	48 hours or less	72 hours	48 hours
Stages seen in peripheral blood	Trophozoites, schizonts and gametocytes	Usually only early trophozoites and gametocytes.	Trophozoites, schizonts and gametocytes	Trophozoites, schizonts and gametocytes
Infected red cell	Enlarged, pale Schuffner's dots	Not enlarged. Maurer's dots	Not enlarged No Schuffner's or Maurer's dots	Enlarged. Pale Becomes oval Schuffner's dots fimbriated.
Number of parasites in red cell	Double infection not uncommon	Infection with 2 or more parasites very common	Double infection very rare	Double infection rare
Young trophozoite	Small and large rings One chromatin dot	Small fine rings Often 2 chromatin dots. Applique forms	Small and large rings One chromatin dot Narrow band forms	Small and large rings Occasionally two chromatin dots
Pigment	Yellow-brown fine particles	Dark brown or black Coarse	Dark brown or black Coarse	Darkish brown Not so coarse
Amoeboid movement	Active	Present	Slight	Slight
Segmenting schizont	Rounded with irregular outline	Oval or round Usually absent from circulating blood	Round or oval	Round
Mature schizont	12-24 merozoites	8-36 merozoites Pigment prominent	6-12 merozoites May be rosette with control pigment	6-12 merozoites Central pigment mass
Size of mature schizont relative to red cell	Almost completely fills enlarged red cell	Occupies two-thirds diameter of normal-sized red cell	Almost fills normal - sized red cell	About three-quarters of diameter of enlarged red cell
Gametocytes	Round Almost fill enlarged red cell	Crescentic May be plump or bean-shaped	Round Fill normal-sized red cell	Round Resemble *P vivax* Red cell enlarged, rarely oval

TABLE III Differentiation of human malaria parasites [From B G. Maegraith, *Pathological Processes in Malaria and Blackwater Fever*, Blackwell Scientific Publications, Oxford, 1948]

TABLE IV

THICK FILM CHARACTERS

Plasmodium vivax, malariae, and falciparum

Stage	*Plasmodium vivax*	*Plasmodium malariae*	*Plasmodium falciparum*
Early Trophozoite	Fairly numerous, irregular cytoplasm, fairly large single chromatin bead, often mixed with later stages	Few, more regular cytoplasm, medium size single chromatin bead, may be segmenters present	Often very numerous, delicate cytoplasm small, sometimes double chromatin bead, no other forms usually present except perhaps crescents
Half-grown Trophozoite	Great irregularity of cytoplasm which tends to scatter away from single chromatin blob, few small granules of pigment	Regular compact cytoplasm contracting around single chromatin bead, pigment forms early and tends to concentrate	Not common in peripheral blood, regular cytoplasmic ring, broken ring, and common patterns, single or double chromatin bead
Late Trophozoite	Considerable cytoplasmic scatter and irregularity, chromatin blob often isolated, fine granular pigment with moderate dispersion and perhaps isolated from cytoplasm, other stages usually present, Schuffner's dots sometimes seen	Numbers generally few, older stages present, rounded, compact, cytoplasm often obscuring chromatin, scattered pigment, relatively abundant	Not in peripheral blood except in very heavy infections, solid, irregularly rounded, chromatin indistinct, pigment concentrated
Early Schizont or Presegmenter	Large amount of cytoplasm loosely covering abundant chromatin which is beginning to segment, pigment granules discrete and lightly concentrated in one or two areas	Smaller and not so numerous, some scatter of cytoplasm and segmentation of chromatin, pigment in small separate granules	Generally not in peripheral blood, but if so will be associated with numerous typical ring forms, irregular, fairly compact, dark staining, pigment fused in a single mass
Mature Schizont or Segmenter	8-16, usually 12-15 merozoites, relatively large size, early vacuole formation, pigment granular and clumped, other stages often present	6-12, usually 8 merozoites, each with vivid purple, ovoid bead of chromatin, early vacuole formation, pigment compact clump of discrete granules, light infection, smaller size	Rare in peripheral blood, 12-24 or more merozoites, fairly uniform ovoid or round chromatin beads, merozoites grouped or scattered, pigment a single, dark mass
Gametocyte	Round or oval, relatively large, with fairly uniform cytoplasm somewhat frayed at edges small rodlet-shaped pigment, irregularly scattered, abundant chromatin, more diffuse in males	Rounded, compact, with abundant peripheral pigmentation in round granules, single chromatin mass often obscured and more diffuse in males	When mature and normal has distinctive crescentic shape, females longer and more slender, with central pigment and chromatin, males fatter and paler, with scattered pigment and diffuse chromatin, coarse rice grain pigment

TABLE IV Thick film characters [From P F Russell, *Malaria*, Blackwell Scientific Publications, Oxford, 1952, after J W Field]

appendicitis or peritonitis, or may simulate pneumonia or pleurisy, especially in cases where spontaneous splenic infarcts or subcapsular haematomata have occurred. Examination of the blood should never be neglected in endemic areas, even in apparently obvious cases If parasites cannot be found in the peripheral blood or if conditions make the examination of blood films impossible, administration of an anti-malarial drug may be of some diagnostic value. Failure to control the fever in three to four days by the carefully supervised administration of specific drugs calls for reconsideration of the diagnosis The presence of quinine, mepacrine or Paludrine can be chemically checked in the *urine*

If facilities for blood examination are not available and malaria is suspected, a full antimalarial therapeutic course should be given

THE TREATMENT OF MALARIA

THE TREATMENT OF THE ATTACK AND COMPLICATIONS

Treatment of the attack consists of specific measures, i e. the use of antimalarial drugs, designed to eliminate or control the parasites, and other measures intended either to assist the action of the specific drugs or to restore the physiological balance of the body.

I. AVAILABLE DRUGS

The following compounds all have their uses in the treatment of malaria

(a) [illegible]

Toxicity in therapeutic dosage Low Occasional gastrointestinal discomfort, sometimes transient pruritus and blurring of vision

(b) *Mepacrine* (Atebrin, Atabrine, Quinacrine) a bitter yellow acridine compound prepared as the hydrochloride or methane sulphonate

The drug is prepared as

(i) *Tablets* containing the equivalent of 100 mg of the base as hydrochloride

(ii) *Powder*, in ampoules for solution in water. Usually the soluble methane sulphonate (musonate 'atebrin musonate') is prepared in doses equivalent to 100 or 300 mgm of the base

Action Mepacrine is a schizonticide acting on the early stages of the asexual cycle of all parasites It can effect radical cure of falciparum malaria. It has an action on gametocytes similar to that of chloroquine

[illegible]

(c) *Proguanil* (Paludrine, Chloroguanide) a colourless bitter synthetic biguanide

The drug is prepared as

(i) *Tablets*, containing 100 mg hydrochloride (ii) *Tablets* containing 25 mg hydrochloride

Action on parasites Proguanil is a schizonticide acting a little later in the life cycle and a little more slowly than quinine or mepacrine It is a causal prophylactic for falciparum malaria, and inhibits the development of the sexual cycle in the mosquito

Toxicity in therapeutic dosage There may be slight gastrointestinal disturbances, including vomiting, and occasional haematuria, with high dosage, but with normal therapy the drug may be considered non-toxic

(d) *Pyrimethamine* (*Daraprim*) the drug is prepared as tablets containing 25 0 mgm of the base

Action Same as Proguanil

Toxicity in therapeutic dosage Very low

(e) *Quinine* a bitter crystalline alkaloid prepared as bihydrochloride, hydrochloride or bisulphate Of these, the first is the most soluble

children

Action Quinine is a schizonticide acting on the early ring forms of the asexual parasite in all infections

Toxicity in therapeutic dosage Some tinnitus, deafness and dizziness may be expected and sometimes nausea, occasionally vomiting

Erythematous rashes (sensitivity) may occur, and quinine may sometimes give rise to haemoglobinuria

In large doses it may promote abortion, this is unlikely in therapeutic doses Very large doses may cause blindness

(f) *Pamaquine* (Plasmoquin, Plasmochine) and *Primaquine* Bitter colourless synthetic 8-amino-quinolines

The common approximately similar doses mixed with various amounts of quinine or Proguanil salts (iii) Primaquine is prepared as tablets containing 7 5 mgm or 15 0 mgm of the active substance respectively

Action The 8-amino quinolines are relatively weak schizonticides In combination with more active schizonticides such as quinine, they may produce radical cure of vivax malaria (possibly by action on the EE forms of the parasite) They destroy gametocytes

associated with a syndrome resembling blackwater fever, sometimes with anuria, may occasionally develop in individuals of coloured races, the tendency is hereditary It is claimed that Primaquine is a little less toxic than Pamaquine

2. THE CHOICE OF ANTIMALARIAL DRUGS

In a given case, the choice of d[illegible]
of action and the point in t[illegible]
maximum effect.

In severe infections the speed of action may be of supreme importance Quinine is generally considered to have the quickest action, and may be the drug of choice in the initial parenteral control of severe or complicated attacks.

Antimalarial drugs should be given orall[illegible]
teral admin[illegible]
by parent[illegible]

Parentera[illegible]
admin[illegible]
r[illegible]
a[illegible] collapse (shock); coma or
d[illegible] hyperpyrexia; hyperparasitaemia; other forms of pernicious malaria

3 DRUG TREATMENT OF THE ACUTE UNCOMPLICATED ATTACK

A IN NON-IMMUNE ADULTS, VISITORS AND FOREIGN RESIDENTS IN AN ENDEMIC AREA

1 *Falciparum malaria* Any of the following courses of treatment will bring about clinical cure and will in most cases produce radical cure. A good drink of water or other bland fluid should be taken with each dose of the drug. Treatment must be followed in an endemic area by suppressive therapy

(a) *Chloroquine*	4 tablets (600 mgm base) on admission
	2 tablets (300 mgm base) 6 hours later
	2 tablets (300 mgm base) once daily for 2 or 3 days
(b) *Mepacrine*	300 mgm t d s. for 1 day
	200 mgm t.d s. for 1 to 2 days
	100 mgm t d s. for 5 days

Mepacrine and Proguanil have been used in combination but Proguanil is now seldom used alone because of its relatively slow action on the parasite, and in view of possible parasite resistance. An example of combined therapy is as follows.

(c) *Mepacrine*	300 mg. t.d s for 1 day
Proguanil	200 mg. t d s. for the following 9 days

(d) *Quinine* Grains 10 (650 mgm) t d s for 2 days
Grains 10 (650 mgm) b i d for 5 days
(Sodium bicarbonate solution may be given after dosage with quinine It is said to assist absorption.)

ii *Vivax malaria* [1] Any of the above courses of treatment will be effective It is often unnecessary to continue them for more than 2 or 3 [illegible] epacrine, [illegible] annot be [illegible] vivax

iii *Relapsing vivax malaria* [1] Combined therapy offers the best chance of radical cure A schizonticide is used to deal with the E form of the parasite and an 8-amino-quinoline with the EE form

(a) *Quinine* grains 10
Pamaquine 8 to 10 mgm (base)
Three times a day *concurrently* for 10 days

(b) *Proguanil* 100 mgm
Pamaquine 8 to 10 mgm (base)
Three times a day *concurrently* for 10 days

(c) *Quinine* grains 10 (640 mgm) thrice daily
Primaquine 7 5 mgm twice daily (or 15 mgm once daily)
Continue for 10 days

The dosage of Pamaquine is given above in terms of the hydrochloride A common salt administered is, however, the naphthoate, the total weight of which equivalent to the dose of hydrochloride (10 mgm) is roughly 20 mgm Primaquine is now commonly used

Mepacrine is not usually given concurrently with 8-amino-quinolines

(*Note* Because of possible toxic effects of the 8-amino-quinolines patients must be kept in bed during treatment and persuaded to drink fluid freely See p 246 and 24)

B IN NON-IMMUNE CHILDREN

All drugs except the 8-amino-quinolines, which are better avoided, are well tolerated by children Chloroquine is probably the most satisfactory The treatment is the same for all forms of malaria

Proguanil may be given in accordance to body weight provided no parasite resistance is anticipated There is a very wide safety margin between therapeutic and toxic doses The following table gives a rough guide

[1] Applies also to malariae and ovale malaria

Age	Total daily dose given for 5 to 10 days, Maximum depending on the size of child
Birth to 1 year	50- 75 mgm
1 to 2 years	75-150 mgm
3 to 5 years	100-150 mgm
6 to 10 years	200-250 mgm
11 to 15 years	300 mgm to adult dose

Mepacrine

Age	Total daily dose given for 5 days; Maximum depending on size of child
6 months to 1 year	50 mgm
1 to 2 years	100 mgm
3 to 5 years	150 mgm
6 to 10 years	200-300 mgm
11 to 15 years	300-400 mgm
Over 15	Adult dose

Quinine Children tolerate quinine very well, but ordinary salts are often too bitter and *quinine ethylcarbonate (euquinine)* is easier to administer

Birth to 1 year give 1/10 adult dose

Subsequently give $\frac{\text{age}}{20}$ × adult dose

(Example at age of 5, dose is quarter of the adult dose At 10 half of the adult dose)

Chloroquine or Nivaquine.

Age		Dose
Up to 1 year	Day 1	½ tablet followed by ½ tablet in 6 to 8 hours
	Day 2-5	¼ tablet once daily
1 to 3 years	Day 1	1 tablet followed by ¾ tablet in 6 to 8 hours
	Day 2-5	½ tablet once daily
3 to 6 years	Day 1	2 tablets followed by 1 tablet in 6 to 8 hours
	Day 2-5	½ tablet once daily
6 to 12 years.	Day 1	2 tablets followed by 1 tablet in 6 to 8 hours
	Day 2-5	1 tablet once daily
12 to 15 years	Day 1	3 to 4 tablets followed by 1 to 2 tablets in 6 to 8 hours
	Day 2-4	1 to 2 tablets once daily

(*Note* 1 tablet of Chloroquine or Nivaquine contains 150 mgm base)

C IN IMMUNES OR PARTLY-IMMUNES THE INDIGENOUS POPULATION IN THE ENDEMIC AREAS AND OTHERS WHO HAVE BEEN FREQUENTLY REINFECTED

In such individuals all forms of malaria are usually mild, and respond readily to treatment

Single doses of proguanil, or mepacrine 300 mgm of chloroquine 300 mgm (base), or of quinine grains 20 to 30 will usually be effective Children receive equivalent doses

More serious cases need treatment similar to that of non-immunes

4 TREATMENT OF SEVERE AND COMPLICATED ATTACKS

Drug treatment is, of course, essential in dealing with complicated or pernicious malaria, and no delay should be tolerated At the same time, *it is imperative to see that the complication itself is treated at once* In some instances, for example in cases of shock or hyperpyrexia, this may be necessary even before chemotherapy can be commenced For details of the treatment of complications, see below

A CHEMOTHERAPY

Chemotherapy is the same for immunes and non-immunes

Parenteral injection of drugs is required

The choice in order of preference lies between intravenous or intramuscular quinine or 4-amino-quinoline, e g chloroquine, and intramuscular mepacrine

Intravenous injections of quinine or chloroquine are the most immediately effective

DOSAGE FOR ADULTS

(a) *Quinine* parenteral quinine may be repeated after 8 hours It is preferable to give the first dose by syringe, the second may be added to a saline drip Not more than two doses should be given in 24 hours *Oral administration of some other antimalarial should be commenced as soon as possible*

(i) *Intravenous injection of Quinine* Quinine (bihydrochloride) grains 7½ to 10 depending on body weight

A dose of grains 10 (640 mgm) is commonly given

The salt is dissolved in 10 to 15 ml sterile water or saline and taken up into a wide bore syringe

The injection is made slowly through a fine needle

(ii) *Intramuscular injection of quinine (hydrochloride)* The salt is taken up into solution in 5 to 10 ml sterile water and injected

with aseptic precautions deep into the gluteal muscles The injection is painful and may occasionally lead to abscess formation.

(b) *Chloroquine (4-amino-quinoline)*

Intravenous and intramuscular dosage is 200-500 mgm of the base. Technique of administration is as for quinine.

A common preparation in wide use is *Nivaquine Soluble* a solution of chloroquine sulphate made up in ampoules containing 5 0 ml, in a total dose of 200 mgm The contents of the ampoule are diluted to 15 to 20 ml with progen-free water and administered as for quinine.

(c) *Mepacrine: Intramuscular injection of mepacrine methanesulphonate (musonate)* When the methanesulphonate is not available, the hydrochloride may be used in a dose of 300 mgm for an adult.

The powder is dissolved in 3 or 9 ml (depending on whether 100 or 300 mgm are to be used), sterile water and the injection made with aseptic precautions into the gluteal muscles. It may occasionally cause abscess

The injection is less painful than that of quinine. It takes a little longer to act on the parasite than intravenous quinine.

The dose may be repeated 8-hourly, until oral administration is possible

Dosage· Adults — 375 mgm, equivalent to 300 mgm hydrochloride, children — 125 mgm, equivalent to 100 mgm hydrochloride

Mepacrine should not be given intravenously.

DOSAGE IN CHILDREN

Parenteral therapy should be given to children with great care. Dosages of quinine and mepacrine are calculated as for oral administration Solutions should be dilute and are preferably given in divided doses over some hours Both quinine and mepacrine are absorbed through the intestine provided there is no prevailing gastrointestinal disturbance. Intravenous injections should be avoided in very young children. In general for children, but not for adults, the intramuscular route is to be preferred in any case

B TREATMENT OF COMPLICATIONS

(a) *ACUTE HAEMOLYSIS AND ANAEMIA*

Transfusion of blood is necessary when the numbers of erythrocytes are

i e

Citr

judged from the red cell count and the patient's general condition. When transfusion is given solely for the purpose of restoring the circulating erythrocyte numbers, one pint given over 1 to 2 hours is usually sufficient Where lysis is proceeding vigorously it may be necessary to repeat the transfusion The amount of blood given must be carefully measured and should be included in the input-output fluid balance chart

Choosing the donor is a particularly important procedure in malaria, where the agglutinin content of the patient's blood is often temporarily disturbed Blood which is apparently of the right group may prove to be incompatible and *it is therefore essential to cross-match the patient's cells and plasma with the plasma and cells of the donor before transfusion*

(b) SHOCK

Patients in whom shock has appeared including those with algid malaria require immediate infusion of fluid to restore the blood volume The first administration should be one pint of plasma, given rapidly, i e in about half to one hour This should be followed by a more slowly administered pint of isotonic saline or isotonic glucose If further fluid is required because of dehydration or salt deficiency, proceed as for replacement of fluid

(c) ACUTE LOSS OF WATER AND SALT

In patients in whom there has been severe loss of fluid from vomiting or from choleraic diarrhoea, replacement of water and salt is essential, [illegible]

hour Subsequent infusions are given more slowly, i e the second pint in half an hour and thereafter by drip at about 4 hours to the pint In cases in whom salt has disappeared from the urine, it will usually reappear after two or three pints of isotonic saline have been administered Further fluid should be given in the form of 'hypotonic' saline made up of mixtures of one pint isotonic saline and two parts isotonic glucose Not more than 6 to 9 pints of fluid should be given in 24 hours (See p 127)

In all cases a fluid input-output balance chart must be kept; infusions must be included in the total input of fluid for the 24 hours

(d) TREATMENT OF OTHER PERNICIOUS COMPLICATIONS

(i) *Cerebral malaria* The neurological and psychological syndromes are treated on general lines Prompt treatment of the underlying malaria will bring rapid relief in most cases, provided the condition is diagnosed early

Refractory headache following recovery from the acute attack may

be very difficult to manage, but relief may sometimes be obtained by the use of nicotinic acid

Mental sequelae require expert psychiatric treatment.

(ii) *Hyperpyrexia* The basic factor here is the same as in heat hyperpyrexia, i e the inhibition of the sweating mechanism and consequent failure of heat loss

Sweating must be re-established and this is best done by reducing the temperature by evaporation of water from the body surface. The [illegible]

usually continues to fall and natural sweating may appear. Subsequent small rises of temperature are common. Return to hyperpyrexic levels should be treated in the same way

(iii) *Bilious remittent fever* Treatment is that of liver insufficiency. Early treatment of the malaria is the only real hope of success.

In the severe case transfusion or infusion of plasma or saline may be necessary, depending on the degree of anaemia, the presence or absence of shock, or the loss of fluid and salt.

(iv) *Malarial dysentery* The ordinary general treatment of acute dysentery is required

(v) *Choleraic diarrhoea* Early treatment of the malaria is required. Replacement of fluid is essential. If shock has supervened one pint of plasma given fast is indicated, followed by saline as required (see section b above) In cases suffering from dehydration or salt deficiency without shock, one pint of saline should be given rapidly followed by further infusion as required The concentration of urinary chlorides should be watched during treatment (see section c above).

5. TREATMENT SUBSEQUENT TO RECOVERY FROM THE ACUTE ATTACK

PROPHYLAXIS AND SUPPRESSION

Patients living in endemic areas must continue prophylactic or suppressive therapy after treatment of an acute attack.

This is unnecessary in non-malarious areas except for special purposes, e g. the suppression of vivax malaria Efficient treatment of falciparum malaria leads to radical cure.

There is usually no need to remove the patient from the endemic area, except after severe, complicated, or frequently repeated attacks

ANAEMIA

Recovery of the erythrocyte content of the blood is usually rapid after treatment of malaria.

Patients in whom severe anaemia persists into convalescence may benefit by blood transfusion One or one half pint of citrated blood given slowly is usually adequate

Iron salts in the ferrous state should be given in anaemic cases Where the anaemia is severe they may be given intravenously

PROPHYLAXIS AND SUPPRESSION

Drug control of malaria in individuals exposed to infection is achieved in two ways

(*a*) by *prophylaxis*, which implies the prevention of infection after the bite of an infective mosquito, and,

(*b*) by *suppression*, which means the suppression of the erythrocyte infection to subclinical levels

In the subject who has not been previously exposed to infection, the ideal is prophylaxis Since no known drug is capable of destroying the sporozoite, true prophylaxis is not at present possible in any form of malaria Proguanil and pyrimethamine, however, have been shown to destroy the P E forms of *P falciparum* and, if given over the pre-patent period, may thus prevent the initiation of the E cycle in the erythrocyte This action is regarded by some as a form of prophylaxis which has been named '*causal prophylaxis*' Since the end effect is the same as that of the suppression plus radical cure which is achieved in this infection by any active schizonticide, the use of this term is not universally acceptable Effective prophylaxis cannot at present be achieved in vivax, malariae or ovale infections, although proguanil has been shown to delay the appearance of the asexual cycle in some experimental vivax infections

Suppression of all forms of malaria may be achieved by the use of Paludrine, mepacrine or chloroquine and, somewhat less efficiently, quinine

In falciparum malaria the proper use of proguanil, mepacrine and chloroquine in suppressive doses leads to radical cure This is not so in other forms of malaria, which tend to relapse after the cessation of suppressive therapy

Individuals known to be already infected with falciparum malaria must be given a full therapeutic course of proguanil, mepacrine or chloroquine before prophylaxis or suppression is attempted

In frequently reinfected individuals in whom some immunity has developed, suppression is usually the only reasonable and easily attainable objective Prophylaxis under such conditions is to be obtained by entomological and other control measures rather than chemotherapeutic methods

Prophylactic or suppressive therapy can be commenced before entry into, and continued for some time after leaving, an endemic area. This is particularly important in the case of mepacrine.

In order to obtain the full effect of any drug, regular dosage is essential

The drug should be taken with ample fluid; there is no contraindication for alcoholic drinks It is best taken during or shortly before the evening meal.

DOSAGE

For most areas, chloroquine (or some other 4-amino-quinoline), proguanil or pyrimethamine, mepacrine or quinine should all be successful if taken regularly in adequate doses. Proguanil-resistant

the development of the sexual cycle in the mosquito, thus reducing the infectivity of local vectors

In the doses recommended the drugs have, despite a common belief to the contrary, no effect on sexual potency or pregnancy.

DOSAGE

1. NON-IMMUNES VISITORS AND FOREIGN RESIDENTS IN ENDEMIC AREAS

(i) *Proguanil*

Adult One tablet of 100 mgm daily

Children Birth to 1 year. 25 to 50 mgm daily; 2 years to 5 years 50 to 100 mgm daily.

Begin at the time of entering endemic area. Continue for 28 days after leaving area

Toxic effects None

(ii) *Mepacrine*

Adult· One tablet of 100 mgm daily.

Children· Mepacrine is not as convenient for children as is proguanil Daily dosage is necessary, but the required division of the standard 100 mgm tablets is not easy. Dosage is calculated on a weight-age basis as follows:

Birth to 1 year; total dosage of 50 to 75 mgm per week in divided daily doses

300 mgm in divided daily doses.

11 to 15 years, total weekly dosage of 300 in 400 mgm in divided daily doses
Over 15 years adult dose

Begin 14 days before entering endemic area Continue for 28 days after leaving area

Toxic eff
after the f
proceeds
excreted in the hair Women often refuse to take it. The colour is sometimes mistaken for jaundice, but can be differentiated from the latter by the absence of coloration of the bulbous conjunctivae

Late effects are rare, but include the development of browny-blue pigmentation of the finger nails and thickening and blue coloration of the skin and mucous membranes, often most easily seen on exposed parts such as the V of the neck, or on the palate Skin eruptions similar to those due to *lichen planus* may also occur

The psychotic effects of mepacrine have not been observed on suppressive dosage

(iii) *Chloroquine (or other 4-amino-quinolines)*

Adult	2 tablets (300 mgm base) given once weekly
Children	Age 1-2 years, ¼ tablet, 3-5 years, ½ tablet Over the age of 6 years, 1 tablet, over 10 years, adult dose

Toxic effects None

(iv) *Quinine*

Adult	1 tablet 4 or 5 grains daily
Children	In proportion

Note Quinine is less efficient than the other drugs and should be used for suppression *only* where other drugs are not available

Toxicity Dizziness, tinnitus with sime degree of accompanying deafness, nausea, sometimes vomiting, skin sensitivity rashes

2 IMMUNES, SUCH AS POPULATIONS INDIGENOUS TO ENDEMIC AREAS

(i) *Proguanil, mepacrine* 300-500 mgm once weekly

(ii) *Chloroquine* 2 tablets once weekly

Some recomm

which it is desirable not to interfere too much with existing immunity.

(iii) *Quinine* grains 10 once weekly

XVIII

MELIOIDOSIS

DEFINITION

STANTON'S disease or melioidosis is due to infection with a bacterial organism of the glanders group, *Pfeifferella whitmori*. The organism is believed normally to affect rodents, from which man sporadically becomes infected The disease in man is rare, and it usually takes the form of a pyaemia, with multiple caseous nodules and abscesses in various organs and tissues. The mortality is extremely high, and the diagnosis is usually made *post mortem*

GEOGRAPHICAL DISTRIBUTION

A few hundred cases of melioidosis have now been recorded in the Far East, apart from these a single autochthonously infected case has been reported in the U S.A

AETIOLOGY

On autopsy of human cases of suspected glanders infection in Burma in 1912, the expected organism *Pfeifferella mallei* could not be found, but a new and distinct organism, later called *Pf whitmori*, was consistently recovered Subsequently further fatal cases of human infection with this organism were disclosed in various parts of the Far East Natural infections with the organism were discovered in rats, rabbits and guinea pigs, cats and dogs, and horses, cows and pigs, in the same areas

Pf whitmori is a Gram-negative aerobe which closely resembles *Pf mallei*, the organism causing glanders It can clearly be distinguished from it by culture on laboratory media, the course of infection in experimental animals, and by agglutination, absorption and complement-fixation tests

The method by which man acquires the infection has not been established, but it is generally thought that contamination of his foodstuffs by the excreta of infected rats is an important one There is no evidence that the disease spreads from man to man, and all human cases are apparently the result of sporadic infection from the natural reservoirs of infection In rats infected with the organism the disease caused by it is a subacute or chronic one, infected rats continue to discharge the organisms over a considerable time in their faeces and urine.

PATHOLOGY

Lesions much resembling those of glanders occur in almost any of the tissues in the body They consist of caseous nodules which form around embolically conveyed foci of *Pf whitmori* infection As the nodules enlarge their centres become necrotic Extensive multiple caseous abscess formation is almost invariably found in the lungs, liver and spleen at post mortem; similar abscesses may be found anywhere else in the body *Pf whitmori* can readily be recovered in pure culture from all the lesions

CLINICAL PICTURE

In view of the varied location, number and size of the abscesses characteristic of melioidosis the detailed clinical picture is extremely variable Broadly, the disease can be divided into two clinical types, the septicaemic, which rapidly is fatal, and the pyaemic which progresses more slowly, and from which a small percentage of patients may recover if their lesions are restricted in number and very superficial in location

The septicaemic type of the disease resembles any other severe septicaemia There is delirium and severe toxaemia, continued fever, and signs of pulmonary involvement The liver and the spleen enlarge There is usually a dysenteric diarrhoea Patients with fulminating infections may die within a few days, those with a less severe septicaemia may survive for periods up to three weeks

The pyaemic type of the disease is more common than the septicaemic Necrotic lesions and abscesses appear one after another in a number of internal organs The lungs are invariably affected early in the condition, the liver is nearly always involved, the genito-urinary tract is commonly the seat of lesions The central nervous system, in common with every other structure of the body, may contain abscesses Pyaemic melioidosis may simulate any of many grave infective diseases It usually ends fatally within two months, but at times may continue over several months or even for a year or more In rare cases of pyaemic melioidosis the lesions occur superficially in the skin, the subcutaneous tissues, and the immediately underlying muscles, bones and joints. These cases may ultimately end spontaneously if assisted to do so by suitable local treatment

TREATMENT

There is no specific treatment Drainage of superficial abscesses should be done where the condition indicates its desirability

XIX

MYCETOMA PEDIS

DEFINITION

MYCETOMA PEDIS, or Madura foot, is a condition due to infection of tissue with fungal organisms belonging to the genera *Nocardia* and *Madurella*. These organisms are normally free-living saprophytes. On establishment in man they cause a localized and chronic progressive granulomatosis, commonly of the foot, with destruction of the affected tissues and the formation of numerous discharging sinuses

GEOGRAPHICAL DISTRIBUTION

Cases of mycetoma pedis have been reported widely throughout the tropical and subtropical parts of all the continents They are most *prevalent in the humid tropics.*

AETIOLOGY

In 1888 an aerobic actinomycete was for the first time shown to be responsible for disease in mammals, in this case it took the form of 'bovine farcy' This organism was named *Nocardia farcinica.* Shortly afterwards a case of human infection with an aerobic actinomycete was recorded, and this organism was named *Cladothrix asteroides*; subsequently it was renamed *Nocardia asteroides* Since then many cases of infection of man with similar aerobic actinomycetes have come to light; still further names have been applied to the organisms recovered from them The identity and the nomenclature of the strains of fungi recovered from cases of mycetoma in various parts of the world are confused, and it would be profitless to discuss them here The genera *Nocardia* and *Madurella* differ from the other actinomycete, *Actinomyces*, which sometimes affects man, in that they normally are free-living saprophytes whereas the latter is an obligatory parasite of mammals, and that they are aerobic and not anaerobic. Species of *Nocardia* are normally found in nature as saprophytes growing on dead organic

sinuses, there are 'granules'. These granules consist of densely-packed tangled mycelia. They vary in colour with the species of organism, and

may be black, grey, white, yellowish, or red The ends of the mycelia located at the periphery of the granules may be clubbed, hence the name 'ray fungus' These fungi are Gram-negative, they are not acid-fast or are only weakly so They can readily be grown on many simple media under aerobic conditions, but their growth is very slow The different species are distinguished by slight differences in their morphology, by the colour of the granules they produce, and on certain cultural differences when grown on special media Some strains have successfully been introduced into laboratory animals, but there is variation in their capacity to infect them

Mycetoma pedis may affect persons of any race, age, or sex Its incidence is sporadic, and the infection does not spread from one person to another It is seen most commonly in the feet of those habitually barefooted, but occasionally affects other parts The infection may [illegible]

hoes when tilling soil

PATHOLOGY

On lodgment and establishment of the fungus in the tissues it slowly grows and the infection radiates into the surrounding tissues There is no tendency to embolic or metastatic spread Both soft tissues and hard tissues are equally involved by the extending infection The resultant [illegible]

numerous areas of necrosis consisting of necrotic cheesy material, there are also numerous loculations of all sizes from which exudes an oily amorphous debris

The histological appearances are those of a caseous necrosis surrounded by granuloma formation containing endothelial cells, giant cells, round cells, and macrophages laden with fat Mycelia are to be found throughout the affected tissue, and the dense mycelial 'granules' are surrounded by numerous neutrophil leucocytes The tissues may be coloured white, yellow, red, or black by the granules, according to the species of *Nocardia* present Hence the names 'black' or 'white' Madura foot

CLINICAL PICTURE

Mycetoma is a localized and not a systemic disease The first indication of its presence is the appearance of a small rounded painless swelling, usually on the dorsum or on the sole of the foot The swelling

slowly enlarges peripherally over many months or years until there is an irregular rounded mass extending throughout the tissues of the dorsum, or of the sole, of the affected foot At any time during this development, but commonly within some months and less often after some years, sinuses develop from the deeper parts of the lesion through the skin to the exterior From these exudes a viscid oily discharge containing



Fig 33 Black Madura Foot
(Courtesy of *British Encyclopaedia of Medical Practice*, Butterworth & Co (Publishers) Ltd, London)

visible mycelial granules, these granules may be hard or soft, and they are coloured according to the species of fungus responsible for the condition Superimposed bacterial infection may cause the discharge from some sinuses to be purulent, but as a rule the discharge from each is not great in amount and it contains but few pus cells. The discharge mainly consists of an oily suspension of amorphous necrotic material

The infection slowly, but steadily, extends to all the tissues of the foot including, at a late stage, bone. By the time the whole of the foot is involved it forms a large tumour riddled with areas of necrosis and

abscess formation, these communicate with each other and to the e
terior by innumerable sinuses The foot becomes club shaped, glob
and useless, but it is painless The lymphatic channels and glar
draining the area are unaffected, except when there is gross seconda
bacterial infection and this is unusual

The inconvenience caused by the useless swollen foot, and the con
quences of inactivity and economic loss, greatly debilitate the patie
who commonly succumbs after ten to fifteen years to some intercurr
disease.

TREATMENT

There is no specific drug treatment At various times potassi
iodide, sulphatriad, and pentamidine have given encouraging resu
in cases of infection with certain of the causative fungi The antibiot
oxytetracycline and carbomycin also appear to control the infecti
and lead to temporary clinical improvement in some *Nocardia* infectio

Diaminodiphenylsulphone (D D S) has been shown to be fung
static in cultures When introduced by local injection or by irrigati
into the lesions, and at the same time administered by mouth, it l
appeared to be of therapeutic value in cases both of *Madurella* and
Nocardia infection It usually has been given together with strepton
cin Complete surgical extirpation of the whole of the fungus-infec
tissues is the only sure cure In practice this usually means amputat
through healthy tissue

XX

NUTRITIONAL DISORDERS

INTRODUCTION

NUTRITIONAL requirements in the tropics are basically the same as in temperate regions. The diet of populations indigenous to the tropics is, however, largely governed by custom and supply and tends to be based on some staple carbohydrate foodstuff, such as rice, corn or cassava to which other substances are added fortuitously. Such a diet tends to be badly balanced and lacking in total protein, especially animal protein, and deficient in many essential substances, including minerals and vitamins. Community-wide poverty and disease, climatic extremes such as droughts and floods and inefficient agricultural methods combine, moreover, to make food supplies inadequate It is not surprising therefore that nutritional disturbances in which any dietary element may be involved are common in the tropics and represent a constant background against which other disease processes develop.

Most nutritional disturbances are directly related to the diet and arise from such factors as inadequate intake, imbalance of the various constituents of the diet and deficiences of essential substances Some, however, may be independent of the diet and originate from faulty intestinal absorption, as in sprue, or from interference with the intake, absorption or utilization of nutrients, arising from parasitic or bacterial infection However they develop, primary quantitative or qualitative deficiencies are potentially injurious to health and may themselves influence the pathological effects of other disease states, especially parasitic infections

Finally, several endogenous food poisons are known or believed to cause clinical disorders such as epidemic dropsy (see p 64), lathyrism, vomiting sickness of Jamaica, and possibly also hepatic veno-occlusive disease.

VITAMIN DEFICIENCIES

CAROTINOL (VITAMIN A)

The preformed vitamin is present in milk (but not in *skimmed* milk, liquid or powdered), cream, animal fat, and in liver and fish oils The precursors, carotenes, are present in highly coloured fruits or vegetables, and in red palm oil Conversion of carotene to vitamin A occurs in

the liver, but not efficiently in infants, particularly if the liver is damaged by protein deficiency as in kwashiorkor

Low grade carotinol deficiency is widespread in both temperate and tropical climates Acute manifestations of the vitamin lack are not uncommon especially in children in areas where the general standard of nutrition is low The deficiency is a potent cause of permanent blindness in southern India, Ceylon and central China

PHYSIOLOGY AND PATHOLOGY

Carotinol has at least two important functions in man, one relating to the synthesis of visual purple of which it forms an integral part, and the other relating to maintenance of epithelia In low grade deficiency night blindness occurs, and if deficiency is long continued or more severe, other changes may follow. In long-continued deficiency, all epithelial structures are affected to varying degree, undergoing a keratinizing metaplasia Loss of ciliated epithelium in the trachea and bronchi increases liability to respiratory infection, the ducts of many small glands become blocked, enlarge, and appear as follicles or retention cysts, involvement of lacrimal glands leads to drying and metaplasia of the cornea (xerophthalmia) and Bitot's spots Actual softening of the cornea (keratomalacia) may occur in severe cases, with perforation, loss of aqueous humour, prolapse of the iris and loss of sight as permanent damage

Carotinol is readily absorbed from the intestines and sufficient may be stored in the liver to last for many months of deprivation Absorption of the vitamin A precursors, the carotenes, occurs less readily and the presence of both fat and bile is necessary Conversion of carotenes to the vitamin takes place in the liver, being more efficient in adults than in children, babies appear able to utilize only the preformed vitamin

The minimum adult requirement is approximately 1300 I U (International Units) a day of the pure vitamin, but at least double this amount is desirable A baby requires about one-quarter and children after the age of 12 years need the same amount as an adult Babies and children should be supplied with the preformed vitamin in preference to carotene, and adults should receive more than the theoretically sufficient amount of carotene owing to incomplete absorption and conversion to carotinol One international unit of carotinol equals in potency *0 6 μg of carotene*

CLINICAL PICTURE

Clinical evidence is present only if the deficiency in the diet is severe and of long standing, and if hepatic stores of the vitamin have been

depleted. The [illegible]

however, affect almost any area except the scalp Of the eye changes, night blindness is the first observable feature but may pass unnoticed Typically, it is more pronounced at dusk than at dawn. Later xerophthalmia develops. The dryness of the conjunctiva is best shown by holding the eyelids open for about a minute, the eye rapidly losing its lustre Keratinizing metaplasia of the cornea now takes place, and is accompanied by smarting, irritation and photophobia. Infection of the conjunctiva may occur at this stage with the production of watery discharge Unless the vitamin is administered, keratomalacia usually,



Fig 34 Carotinol (Vitamin A) deficiency The skin of the neck is dry and is generally thickened the hyperkeratotic papules are well marked
[Courtesy Roche Products Ltd]

but not invariably, follows, with distortion and vascularization of the cornea, and the development of corneal opacities If bacterial invasion has occurred the condition can progress with alarming rapidity and perforation of the cornea may be a sequel. Provided treatment is instituted before the occurrence of perforation the condition is largely reversible, but corneal distortion is permanent Acute eye conditions are commonest in infants in whom there is a considerable mortality from bronchopneumonia.

Slighter, long-continued carotinol deficiency appears to result in the production of Bitot's spots which usually look like 'a dab of chalk paste striated with a pin' but sometimes have a foamy appearance. They usually appear just external to the cornea Night blindness may or may

not be present These spots do not ulcerate and have no clinical significance except as indicators of deficiency

Skin changes The skin appears dry and rough; later a local eruption may appear consisting of sharply defined dry horny papules, round or oval in shape, and varying in diameter from about 1 to 5 mm In the early stages the lesion is more easily palpated than seen, and the papules increase in size as the deficiency continues Typically the eruption occurs first on the fronts and sides of the thighs, on the front of the arms and shoulders, and on the extensor surfaces of the forearm, it may, however, occur in most areas but the scalp is spared It resembles that seen in scurvy, but perifollicular haemorrhages are not present Secondary infection and ulceration are rare, pruritus is less so The skin condition is known by many names, the commonest being shark skin, toad skin and phrynoderma

DIAGNOSIS

There is no field test for carotinol deficiency and diagnosis should be made on clinical grounds supplemented by a therapeutic test Keratomalacia and inflammation of the cornea may be due to deficiency of the B group of vitamins, trauma or severe conjunctivitis arising from other causes Both eyes are not necessarily equally or simultaneously affected in carotinol deficiency Associated skin lesions may be present giving a guide to the true aetiology of the eye lesions The skin eruption has to be differentiated from that occurring in protein malnutrition or scurvy

TREATMENT

Administration of the vitamin itself is essential in the treatment of children, or of adults suffering from acute manifestations When the deficiency is less marked it may, in the case of adults, be treated with carotene using such sources as red palm oil

Eye conditions The standard dose of carotinol suggested is 20,000 I U for children, 80,000 I U for adults Night blindness responds rapidly to a single oral dose Xerophthalmia should receive a daily oral dose until improvement has set in In the case of keratomalacia the first dose should, if possible, be a vitamin concentrate administered subcutaneously Oral therapy, as for xerophthalmia, should then be instituted Should parenteral therapy be impossible, instilling cod liver oil drops into the eye may be of assistance It is also important to control ocular bacterial infection by instillation of eye drops such as penicillin, 5 per cent sulphacetamide, or 0 5 per cent zinc sulphate Bitot's spots disappear slowly on a prolonged dosage regime, such as that recommended for skin changes

Skin changes Administration of carotinol may be necessary over a period of months before the skin eruption disappears, although the skin becomes less dry, and sweating is restored within 2 to 3 weeks Adults and children over 14 may require 40,000 I.U. or more a day, infants needing a quarter of this amount; a lower dosage than this is usually effective but will have to be given for a longer time.

CALCIFEROL VITAMIN D

Calciferol, which is concerned with efficient absorption of calcium from the gut, is present in fish oils, milk and eggs and is synthesized in the skin in sunlight, from its precursor, 7-dehydro-cholesterol Like vitamins A and K, it is fat-soluble and its metabolism is therefore adversely affected by syndromes interfering with absorption of fat.

RICKETS

Rickets is adequately described in many standard text books of medicine, and is therefore only mentioned here Nevertheless it is an important tropical nutritional deficiency syndrome, and is more wide- [illegible]

absorption, and exclusion of sunlight – may combine to cause rickets In the tropics, rickets is less common in rural areas than in towns, where children play in the shadow of buildings and where women confined in purdah may suffer osteomalacia as a result of depletion of their calcium reserves by successive pregnancies.

DIAGNOSIS

The clinical picture of rickets is readily recognizable, but skull bossing may be due to sickle-cell anaemia or thalassaemia (see p 323).

TREATMENT

One single injection of 300,000 international units of calciferol may be given to severe cases unlikely to attend or be brought for much smaller daily dosage of an oral preparation of vitamin D Prolonged high dosage of Vitamin D may lead to calcification of renal tubules

THE B GROUP OF VITAMINS

Members of this group are essential components of enzyme systems on which cell metabolism depends Thus, thiamine is known to be concerned with removal of pyruvic acid in the end stages of carbohydrate metabolism, while riboflavine and nicotinic acid are involved in tissue oxidation B vitamins are therefore provided by highly cellular food, e g liver and yeast, and conversely, a diet lacking in any one is likely to lack in the others

Although deficiency syndromes due to a lack of a single vitamin are uncommon it is useful to give a separate account of the clinical significance of each vitamin of importance in the tropics Synthesis of some vitamins by the intestinal bacteria takes place

THIAMINE (Vitamin B_1, Aneurin)

Although the biochemistry of thiamine has been worked out in some detail, little is known of the clinical effects in man of specific thiamine deficiency

The requirement of thiamine is related to carbohydrate metabolism, and is approximately 0 6 mg per 1000 non-fat calories of diet A daily intake of about 1 mg is desirable, 3 mg in pregnancy

THE BERIBERI SYNDROMES

AETIOLOGY

The beriberi syndromes result from lack of several factors, the chief being that of thiamine The syndromes are found especially in the Far East among peoples whose staple food is polished rice The onset of the syndrome may be precipitated by infections, by pregnancy and by hard manual work

PATHOLOGY

The cellular changes seen at autopsy are largely those of starvation, and are not pathognomonic of beriberi In dry beriberi muscular atrophy is marked, but this is not so evident in wet beriberi where oedema and serous effusions may mask the wasting Evidence of acute cardiac failure may be present, i e oedema especially of the legs, pulmonary congestion and oedema; and congestion and centrilobular degeneration of the liver which may be enlarged The heart is frequently hypertrophied and dilated, the right side being more affected than the left, and the cardiac muscle may show signs of degeneration

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be present Physical examination reveals an irregular pulse, tachycardia, an enlarged heart especially on the right side and, commonly, systolic murmurs Abnormalities of the electrocardiogram are usual The liver may be enlarged and tender The individual may die suddenly from cardiac failure

Cardiac and other forms of adult beriberi In thiamine lack the heart is probably always affected, and acute heart failure may develop during the course of either dry or wet beriberi Cardiac beriberi may arise in an individual who is apparently healthy, although some neurological evidence of the disease is nearly always present It may be precipitated by hard manual labour

Acute beriberi is a well defined syndrome in which there is a sudden onset of both cardiac and neurological signs The syndrome frequently ends in death, but more usually progresses to the chronic dry form

Thiamine deficiency can arise in chronic alcoholism The alcohol supplies an appreciable number of calories, and at the same time gives rise to gastritis Anorexia results, and the diet taken may be very inadequate, leading to a polyneuritis which is largely amenable to beriberi therapy

Wernicke's encephalopathy may complicate the picture, associated [illegible]

[illegible]

[illegible]

[illegible]

is characterized by anorexia, vomiting and oedema Neurological signs are not common Aphonia may occur leading to a 'plaintive whine which is almost pathognomonic' Later signs of intracranial pressure occur with convulsions, meningismus and later, coma Convulsions may be the first sign, and the infant dies shortly after with acute cardiac failure Some authors believe that true convulsions do not occur, and that the spasmodic muscle contractions are due to abdominal pain The disease is probably associated with a lessened excretion of thiamine in the milk of the mother, though only 50 per cent of the mothers show clinical beriberi There is now some evidence to suggest that there are metabolic products in the mother's milk which are toxic to the infant

DIAGNOSIS

The manifestations of beriberi are protean and each case must be considered separately Neuritis is the most constant feature, and is best demonstrated by squeezing the calf muscles, which become painful Loss of muscular power is shown by asking the individual to rise from squatting without the use of hands, and the loss of co-ordination by

The peripheral neuritis may be accompanied by Wallerian degeneration, and nerve degeneration within the central nervous system and retina have been reported Congestion and atrophy of the upper part of the alimentary tract may take place.

Evidence of deficiency of other vitamins may be present, such as *cheilosis*, skin changes, spongy gums, stomatitis and corneal vascularization.

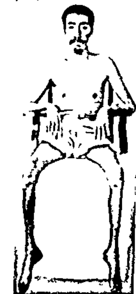


FIG. 35 Thiamine deficiency 'Dry' beriberi, showing wrist-drop, foot-drop and marked wasting of the lower extremities [Courtesy Roche Products Ltd]

CLINICAL PICTURE

Beriberi is usually chronic, but can develop with alarming rapidity. Signs and symptoms do not occur until the individual has been on a poor diet for three months or longer.

Chronic dry beriberi. Early signs and symptoms include fatigue; a feeling of heaviness and stiffness of the legs; areas of paraesthesia may be present Later, headache, insomnia and anorexia develop, commonly with dyspnoea and palpitations. The muscles become painful to pressure.

After a varying length of time the major signs of the syndrome develop. The chief of these is an ascending symmetrical bilateral peripheral neuritis, with weakness, cramps and muscular wasting. The gait becomes ataxic, and the aid of a stick is commonly invoked. Foot drop, followed by wrist drop, may occur; the hand grip becomes weak and fine movements of the fingers are no longer possible There is often a loss of sensation over the tibiae, and the individual may complain of burning feet. The achilles and patellar reflexes disappear, frequently after a period of augmentation Paralysis of the lower limbs may occur sphincter control is maintained until very late in the disease

Chronic wet beriberi The main features of this disease may be similar to those of dry beriberi, but oedema is prominent The oedema is most frequent in the lower limbs, but in the early stages may be present in other parts of the body Serous effusions occur Muscular wasting is commonly masked by interstitial fluid, but weakness and the neural signs are usually seen

In addition, the cardiac signs are usually more marked than in the dry form Dyspnoea and palpitations are marked, precordial pain may

photophobia have all been described and may be relieved by administration of riboflavine alone On the other hand none of these findings is pathognomonic of riboflavine deficiency They may be due to lack of other vitamins, local infection and metabolic disturbances

The daily requirement is related to the amount of carbohydrate eaten, but may be estimated as roughly 0 4 mg per 1000 calories Therapeutically 50 mg daily may be administered intramuscularly, but 15 to 20 mg daily by mouth will usually produce a clinical response

NICOTINIC ACID

Lesions apparently due to deficiency of nicotinic acid are related to the skin mouth tongue, oesophagus and vagina The initial change in



FIG 36 Multiple deficiency of the B_2 group of vitamins
Nicotinic acid deficiency is shown by the skin changes on the cheeks, thorax and upper limbs There is also cheilosis and angular stomatitis indicative of a riboflavine lack
[Courtesy Dr D B Jelliffe]

the skin appears to be a dilation of the blood vessels in the corium – corresponding to the erythema seen clinically, hyperkeratosis and parakeratosis of the epithelium follows The sebaceous glands become atrophic, whilst the sweat glands remain unchanged Separation of the epidermis from the corium with formation of bullae may occur. These changes are accentuated by noxious stimuli such as pressure,

asking him to shuffle cards, or to do up buttons Testing of reflexes may not be of great assistance, but in many cases local areas of anaesthesia may develop on the shins. Beriberi should be considered in all cases of acute cardiac failure occurring in areas where rice is the chief item of the diet. If there is doubt, it is advisable to treat with thiamine, and the response will clinch the diagnosis Albuminuria does not occur, thus differentiating the condition from oedema of renal origin. Pyruvic acid accumulates in the blood. The diagnosis of infantile beriberi is likely to be missed and is frequently difficult to make. The response to thiamine is rapid, and the therapeutic test may therefore be tried.

TREATMENT

The first essential is to put the patient to rest Other general treatment includes giving an adequate diet, high in protein, and the administration of yeast, 1 to 4 ounces a day.

The amount of thiamine given depends on the acuteness of the syndrome Severely ill cardiac patients should receive 100 mgm of thiamine intravenously, given slowly over the course of 10 or more minutes, using a syringe with a narrow bore needle It is inadvisable to administer by means of an intravenous drip owing to the danger of overloading the heart. A second injection may be necessary, after which 50 mg by mouth should be given daily until recovery. Less acutely ill patients should have 20-50 mg by mouth, and mild cases 10 mg by mouth. The vitamin should be repeated daily until there is considerable improvement

The cardiac response is rapid, and within hours there may be a slowing of the heart, and a steadying of the pulse. The rapid onset of diuresis is characteristic The neural response is much slower; improvement continues for weeks or even months, and may never be complete.

Infantile beriberi, in the stage of cardiac failure, represents a medical emergency The affected infant may require the aid of an oxygen tent Thiamine (aneurin) 25 mgm should be given intravenously, or 50 mg intramuscularly, and the intramuscular route and dose continued for 3-4 days, followed by 10 mg orally daily for weeks During the acute stage, the baby should have artificial feeding, while the mother is given thiamine 50 mg intramuscularly daily and instructed in diet correction

RIBOFLAVINE (Vitamin B_2, Vitamin G)

Lesions due to deprivation of this vitamin in man have not been extensively studied. Cheilosis, angular stomatitis; seborrhoeic dermatitis of the alae nasi, naso-labial folds, eyelids and ears; glossitis, with a magenta tongue; vascularization of the cornea; lacrimation and

Later the major signs and symptoms develop and are related especially to the skin, the alimentary tract, and central nervous system

The skin The skin changes are almost always symmetrical in their distribution An erythema appears, especially in areas subjected to the trauma of sunlight, tight or chafing clothing The erythema may be followed by blistering and hyperkeratosis Pigmentation occurs later, being more obvious in fair-skinned races, and is followed by skin atrophy The atrophic skin is thin and inelastic, and fissures develop in it, leading to so-called crazy pavement dermatitis Widespread desquamation, as seen in the lesions of kwashiorkor, is unusual Exudation and crusting may occur in the fissures When fully developed the appearance of the skin in dark races is (as has been aptly described) as if the skin had been painted with dark enamel which has cracked and, in places, chipped off This appearance is especially marked on the forearms and over the shins

The eczematous skin condition due to riboflavine deficiency may be present on the face and scrotum

The alimentary tract Cheilosis, stomatitis and glossitis are usually present, and the papillae of the tongue become atrophic The colour of the tongue varies between red and magenta Indigestion, heartburn, anorexia and flatulence are common, and diarrhoea is one of the most constant features of the disease Owing to intestinal hurry undigested food is passed in the faeces which may contain an increased amount of fat

Nervous system Mental confusion, dullness, and even dementia may occur, Dementia only occurs in cases of long standing and may be irreversible Headache, vertigo and depression may be present in the early stages

Nerve palsies are uncommon but may occur Burning feet and numbness are included in the subjective complaints

Course Various other deficiencies including those of ascorbic acid, folic acid and iron may arise, being aggravated by the occurrence of anorexia Untreated pellagra usually lasts five years or longer before death supervenes Minor, non-fatal cases of the syndrome are common

DIAGNOSIS

The symptoms of early pellagra are vague, and unless the diagnosis is considered the syndrome may be missed, but soreness of the mouth and tongue is common Yeast (1 to 4 ounces daily or yeast products such as Marmite (1 to 3 teaspoonsful daily) may be added to the diet

but is more chronic

sunlight and burns. In the mucous membranes listed above vaso-dilatation with atrophy of the epithelium occurs. The daily requirement of nicotinic acid is in the region of 10 mg

THE PELLAGRA SYNDROMES

Pellagra is due essentially to a lack of nicotinic acid and protein Associated deficiencies, especially of the B group of vitamins, are almost invariably present, and the clinical picture may therefore vary considerably Although pellagra has been reported from many parts of the world, it is especially prevalent in maize-eating populations The reason for this is twofold Firstly, there is, in maize, a substance rather similar in chemical constitution to nicotinic acid This substance acts as an antivitamin and, whilst replacing nicotinic acid in enzyme systems, it cannot carry out its functions If sufficient nicotinic acid is present in the diet the replacing action is unimportant. Secondly, maize is deficient in tryptophane, an amino acid from which nicotinic acid can be synthesized in the body Provided sufficient animal protein is present in the diet pellagra cannot develop

CLINICAL PICTURE

The disease is chronic and typically has a seasonal incidence, coming on in early spring, waning in the summer only to return with increased severity the next year Early indications of the disease are vague and include anorexia, weakness, loss of weight, gastrointestinal disturbances and soreness of mouth and tongue.

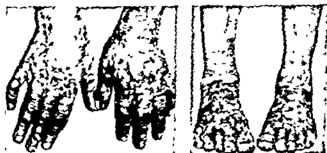


Fig 37 Nicotinamide deficiency
Typical skin lesions of severe pellagra, showing coarse desquamation and pigmentation of the hands and feet.
[Courtesy Roche Products Ltd]

The action of B_{12} is not understood It is apparently necessary for the synthesis of nucleic acids, and it probably enables the body to utilize conjugated folic acid which otherwise would be unavailable for erythropoiesis, and whilst nearly all macrocytic anaemias respond to folic acid, B_{12} is sometimes ineffective It is uncommon for an anaemia to respond to B_{12} and not to folic acid

There is, as yet, scant evidence that a dietary deficiency in vitamin B_{12} occurs in man Human requirements are low, and one microgram daily is probably sufficient bacterial synthesis in the gut may produce far more than this Lack in man appears to be due to a defect in absorption, which is probably due to a lack of Castle's intrinsic factor Therapeutically 10 µg parenterally will produce the maximal blood response in pernicious anaemia, and 50 µg weekly are usually sufficient for maintenance

VITAMIN C ASCORBIC ACID

Ascorbic acid is said to be necessary for the formation of the intercellular 'cementing' substance (especially that of the fibrous cells) and in deficiency the mesenchymal cells may separate On this theory the haemorrhages, breaking down of scars, and delayed healing of wounds are readily explained

There are no constant biochemical or cellular changes in the blood, and a low concentration of ascorbic acid is not necessarily indicative of ascorbic acid deficiency

SCURVY

Scurvy is a deficiency syndrome primarily due to lack of ascorbic acid Associated deficiencies, especially of thiamine and carotinol, are not uncommon, and the haemorrhagic tendency of scurvy may be due to citrin (Vitamin P) deficiency Pure ascorbic acid deficiency does not produce a deficiency pattern identical with that commonly seen clinically

Daily requirements are of the order of 10 mg daily for adults, but more is desirable the requirements for children are not known but estimating on a weight basis, they are relatively higher than for adults

The majority of the morphological changes are obvious from the description of the clinical signs In addition, in children there is deficient dentine and bone formation The latter may be seen radiographically, and there is a wide zone of calcified but non-ossified material just beneath the actively growing epiphyseal cartilages – the scorbutic lattice Fractures may occur in this area

TREATMENT

In the early stages dietary changes alone may suffice to cure the disease, and in any case therapy with vitamins should be supplemented by a better diet

(1) Multiple vitamin therapy. The treatment for a severely ill pellagrin is: Nicotinamide 500 mg by mouth daily for 3 to 4 days followed by 200 mg daily for a further 10 to 15 days. The vitamin may [illegible]

acid is given Riboflavine 10 mg daily and ascorbic acid 100 mg daily by mouth for 7 days are also required. If the symptoms persist, a single dose of 50 mg pyridoxine may be tried after a week

Less severely ill pellagrins respond to a dose of 100 to 200 mg nicotinamide daily for 10 to 15 days. Riboflavine and ascorbic acid should also be given, as above

(2) Dietary therapy. This should be instituted slowly and if diarrhoea is very acute, slow intravenous administration of casein hydrolysate or plasma (1 to 3 pints daily) is advisable for the first few days When the diarrhoea permits, the diet should include milk, eggs, liver, meat, fresh vegetables and yeast extracts or yeast (up to 4 ounces daily). It should be noted that milk is a good source of tryptophane.

FOLIC ACID (*Vitamin M, Vitamin B_c*)

In the absence of available folic acid, the bone marrow suffers megaloblastic arrest, resulting in a macrocytic anaemia which responds specifically to folic acid. Leucopenia and thrombocytopenia may also occur The relationship between the actions of folic acid, B_{12}, and various other substances is very imperfectly understood, but they have, on occasion, the same haematological action. Folic acid appears to be the chief factor in preventing macrocytosis, and the other factors, such as B_{12}, appear to act by facilitating the action of folic acid. This is considered further in the sections on anaemia and on Vitamin B_{12}

Daily requirements of folic acid are not known, and considerable *intestinal synthesis may possibly take place in normal individuals.* Therapeutically a dose of 10 mg twice a day by mouth appears sufficient it may be administered parenterally.

CYANOCOBALAMIN (Vitamin B_{12})

There are at least five closely related substances with the physiological actions of Vitamin B_{12} proper, and which are usually denoted by the name of B_{12} Lack of available vitamin gives a bone marrow and blood picture similar to that of folic acid deficiency. In addition B_{12} lack gives rise to degeneration of nerve tracts within the spinal cord

the proportion excreted, is not very helpful. Of the earlier signs the appearance of perifollicular haemorrhages is the most important and is almost pathognomonic The normal clotting and bleeding times, erythrocyte, leucocyte, and platelet counts, exclude many of the haemorrhagic blood diseases Administration of ascorbic acid as a therapeutic test is advisable in doubtful cases

TREATMENT

Mild scurvy is not a dangerous condition, but all patients should be treated rigorously and immediately, and kept at rest until the acute condition has subsided Although improvement may be expected on only 10 mg ascorbic acid, it is advisable to give 1000 mg, or more orally, either as a single dose, or, preferably, in divided doses, and to supplement the diet with fresh fruit juices, green vegetables and salads When these are not available, sprouting legumes should be substituted Associated deficiencies should receive appropriate treatment, preferably by dietetic means Improvement is rapid

INFANTILE SCURVY

(Barlow's Disease)

This form of scurvy may occur in infants who are given artificial or over-cooked foods It is rare before the sixth month, as the new-born have adequate stores of ascorbic acid The onset is gradual, with the child being fretful and refusing its food. The infant resents handling, as the limbs become very tender, due to painful epiphyses, and subperiosteal haemorrhages The latter show as hot, red, tender swellings near a joint The teeth and gums may remain unaffected When these haemorrhages occur near the femoral necks, rigidity and pseudoparesis of the affected limbs may develop

The condition should be distinguished from acute rheumatism The ascorbic acid therapeutic test may be applied using an oral dose of 50 mg, and X-rays reveal a dense epiphyseal line and sub-periosteal haemorrhages

Treatment consists of 50 to 100 mg ascorbic acid daily by mouth, until recovery (usually a few days) Fruit juices should be added to the diet

KWASHIORKOR

This name, which means roughly 'the deposed one', is given to a malnutrition syndrome first described in Ghana The condition appears

CLINICAL PICTURE



Fig 38 Ascorbic acid deficiency
Scurvy in a man of 52 years showing severe gingivitis The patient was unable to chew hard food because of loosening of the teeth
[Courtesy Roche Products Ltd]

apathy, which are due to associated deficiencies, and the patient definitely feels ill. The gums are proliferative, soft and spongy, and they bleed readily on slight abrasion, the teeth become loose and may even fall out The breath becomes foul from buccal infection

Haemorrhages, other than those already described, may occur The common sites are into or near joints, especially those subjected to trauma; subcutaneous haemorrhages, epistaxis, melaena and haematuria have been reported, but only occur in the well developed syndrome *Old healed wounds become livid and may break down The signs of mild beriberi may also be seen. Gastrointestinal disturbances are infrequent.*

Course Unless ascorbic acid is given, scurvy is a progressive disease. It may terminate suddenly in a cardiac crisis, or from a massive haemorrhage, but death usually occurs from cachexia and intercurrent infection. Such severe scurvy is rare.

DIAGNOSIS

Well developed scurvy is easily diagnosed on the basis of skin and mouth changes *Anaemia is not necessarily present.* The Harris saturation test, i.e. giving a large dose of ascorbic acid and measuring

about an inch or so below the costal margin The spleen may also be palpable in infants with malaria

Changes in the hair and skin are notable The hair becomes grey and depigmented or, especially in Africans, somewhat light-reddish The natural curl is lost, a feature particularly obvious in Africans, in whom the thick rich curl is replaced by a fine grey slightly wavy wisp. It should be noted here that, contrary to many accounts of the syndrome, the reddish discoloration of the hair is not a pathognomonic feature of the syndrome

In the first descriptions of kwashiorkor, well-advanced dermatosis was regarded as an essential part of the clinical pattern This is not so, although slight changes in pigmentation and texture of the skin probably occur in all cases As a rule, by the time the child is seen, extensive dermatoses have developed These appear mainly in areas of the body exposed to irritation and trauma, for instance the buttocks and 'napkin' area, the back, the thighs and legs The lesions are not unlike those of pellagra, but as a rule the areas affected in pellagra, such as the face, hands and feet escape in kwashiorkor Trowell has described the early hyperpigmented lesions as 'black varnished patches' which rapidly enlarge, crack and tend to peel off in 'enamel-paint' plaques up to an inch across, leaving depigmented, thinly epithelialized or ulcerated areas beneath, which may become extensively infected leading to bullous changes and severe ulceration These changes are particularly common over the buttocks and lower trunk On the legs the scaling is often less obvious, the general appearance being that of 'crackled' or 'crazy pavement' skin Many children exhibit in addition dry, slightly scaling skin changes over the greater part of the body surface Changes in the eyes, lips and tongue resulting from multiple specific deficiencies such as Bitot's spots, angular stomatitis, cheilosis and glossitis, occur at all stages of kwashiorkor Photophobia is common



FIG. 39 Kwashiorkor Patchy depigmentation of the skin over the lower limbs
[Courtesy Dr D B Jelliffe]

The child usually suffers severely from gastrointestinal upsets Diarrhoea is usual, with liquid or porridgy, yellow or bile-stained stools containing undigested food, offensive steatorrhoea may occur Vomiting is common and sometimes persistent Varying degrees of

in infants, especially those recently weaned, or being weaned, and placed on staple largely carbohydrate diets such as cassava or rice.

The most important aetiological element is protein deficiency due to low intake Many authorities consider that associated relative excess of

Secondary vitamin deficiencies usually develop Protozoal and helminth infections further complicate the picture

Pathological changes in the skin occur but vary considerably from one patient to another. Patchy variation in pigmentation is common; in dark skins there may be either hyper- or hypo-pigmentation Dermatoses present histological features similar to those occurring in specific vitamin deficiencies. Loss or change of hair pigment, especially in black haired races, is common

The liver in early cases often shows peripheral lobular fatty degeneration and infiltration, which regresses with treatment In more advanced cases there is fibrosis and sometimes well-developed cirrhosis There is often atrophy of the acinar cells in the pancreas, with loss of granules Periacinar, perilobular and even periductal fibrosis is present in some cases In severely affected cases there is a corresponding reduction in duodenal enzyme content, involving especially amylase, lipase and trypsin Other acinar glands may be affected, for instance, the salivary glands. Atrophic changes in the small intestinal wall and hyaline lesions of the glomeruli of the kidneys and pericapsular fibrosis have been reported

The clinical picture is variable It includes retardation of growth, changes in pigmentation in the skin and hair, alterations in the texture of the hair, oedema of the limbs and body, apathy, irritability and pathological changes in certain organs especially the liver and pancreas. Dermatoses derived from nutritional disturbances may or may not be present.

The child is retarded in stature and weight for its age The muscles are wasted but this may be masked by the considerable oedema, which often makes the child relatively heavy; the true state of affairs may be revealed only after the disappearance of the oedema

The patient is peevish, grizzling and apathetic The oedema involves the legs and may extend to the thighs, genitals and buttocks, and at times even the anterior abdominal wall There may be some evidence

changes in infantile cirrhosis The cause is unknown; a virus infection is suspected The developed clinical picture should present no difficulties

TREATMENT

Severe kwashiorkor should be treated in hospital The object is to restore the nutritive balance and deal with parasitic and other infections

In severely dehydrated infants the fluid/electrolyte balance must be adjusted immediately by parenteral saline injection The intravenous route is the most suitable, but subcutaneous, intraperitoneal or bone-marrow techniques of administration may be employed if necessary An infant can safely be given a litre by intravenous drip over the first 24 hours It is seldom necessary to give parenteral fluid after the first day Critically ill patients may be given human plasma or protein hydrolysates intravenously in small volumes, of about 100 ml, for the first few days

Most cases will respond to oral treatment

The diet must be acceptable, easily digestible and rich in protein Fat (especially milk fat) and sugar must be limited to begin with, since they may both provoke diarrhoea Calories can be increased in early treatment by the addition of vegetable fats such as olive oil, which are well tolerated

Skim milk or lactic acid milk constitute the usual basis for the diet In the severely ill infant, the total protein intake should at first be limited to 40 to 50 gm per day, and increased slowly Otherwise the child should be given skim milk or mixtures of skim milk and some

milk protein 3 to 5 gm per kilo body weight Unless there is severe diarrhoea, he advises 3-hourly feeds of a mixture of calcium caseinate 50 gm plus skim milk powder 50 gm, made up in water to 1 litre Where there is diarrhoea the milk should be temporarily withdrawn, as the contained lactate will aggravate the condition)

As the condition improves, the diet is gradually adjusted to one containing adequate protein in normal proportions, other ingredients, such as fruit juice, are added

The protein should theoretically be best supplied from animal sources but this is usually impossible for economic and social reasons, and some form of balanced vegetable protein mixture, derived from local resources must be provided, for example, from ground nut extract and soya bean At this stage it is essential to teach the parents to provide and prepare the diet, otherwise relapse is more than likely.

dehydration may result from loss of fluid and electrolytes from the diarrhoea and vomiting In very severe cases the dehydration may become extreme. Most cases present with mild orthochromic normocytic anaemia Occasionally there may be macrocytosis, associated with increase in number of reticulocytes Megalocytes do not occur. The blood picture to a large extent is decided by the parasitological state of the child, malaria and hookworm may greatly complicate the situation. The bone marrow response is normoblastic.

The serum total protein is low. It may be very low, especially in severely oedematous cases Albumin is reduced; globulins may be increased

The untreated case steadily progresses. There is a very high mortality Fortunately the response to treatment is extremely good, and all but the worst cases have a good chance of survival. The difficulty is that on discharge from a hospital, the baby goes back to a social environment in which the return of the syndrome becomes almost inevitable.

Diagnosis of kwashiorkor is largely clinical The age and dietary history of the infant are the essential points. Retarded growth, oedema, pot-belly, changes in the hair and skin establish the diagnosis. Biopsy of the liver may reveal the fatty or fibrotic changes depending on the stage of the syndrome

Kwashiorkor must be distinguished from other causes of oedema, enlargement of the liver and skin changes. A very careful examination for evidence of parasitological infections is essential.

Kwashiorkor must also be clearly distinguished from marasmus arising from overall malnutrition or from other causes, such as infective states In marasmus the child is grossly underweight; subcutaneous fat is lost, making the skin very thin to the pinch and giving the child the typical features (sunken eyes, skin stretched over the malar regions, prominent bony prominences, relatively protuberant abdomen, etc), there is gross wasting of the muscles. The picture closely resembles that of severe dehydration, but the mouth, lips, etc may remain moist unless diarrhoea appears There is usually no oedema Changes in the skin and hair do not develop *per se* Fatty and other changes in the liver are rare The pancreas is normal

It may at times be necessary to differentiate kwashiorkor from certain stages of hepatic veno-occlusive disease (p 257) and, in India, infantile (biliary) cirrhosis. The latter condition affects infants and young children, often of vegetarian families in good economic circumstances, and is characterized by enlargement of the liver and usually of the spleen, protuberant abdomen with prominent superficial veins, sometimes ascites and oedema and varying degrees of light or severe jaundice. In the late stages there is periportal and diffuse disorganizing hepatic fibrosis with signs of portal hypertension There are no skin

produce iron-deficient anaemias, response results only from the specific chemotherapy

Haemolytic anaemias, usually with a microcytic or normocytic hypochromic blood picture, but occasionally slightly macrocytic, arise from various causes including malaria and haemoglobinopathies (see pp 315-25) Hypersplenism developing in kala azar or in a portal hypertensive syndrome due to schistosomal infection (possibly even to malaria) may similarly lead to anaemia In such cases the basic pattern is often confused by associated protein deficiencies and lack of essential haemopoietic substances

In holoendemic or hyperendemic territories falciparum malaria is often the most important single factor in the production of erythrocyte destruction, especially in pregnant women, who, in the latter months, develop a severe normocytic or slightly macrocytic anaemia, which usually fails to respond to iron therapy but may often respond dramatically to a therapeutic course of antimalarial drugs

Frankly macrocytic anaemia in the tropics is usually associated with megaloblastic erythroid precursors

Megaloblastic anaemias are characterized by macrocytic normochromic or hyperchromic erythrocytes, megaloblastic erythropoiesis, usually leucopenia and thrombocytopenia When the aetiological factor is known, there is rapid response to specific therapy, as in pernicious anaemia upon the administration of the extrinsic factor vitamin B_{12} The causes in the tropics are sometimes ill-defined Megaloblastic anaemias are again common in pregnancy Most of them have an element of iron-deficiency and some limited clinical improvement may result from iron therapy The megaloblastic element, however, responds only to vitamin B_{12} or to folic acid, or to both, depending on the basic erythropoietic discrepancy involved Some cases in Africa have been found to respond also to penicillin therapy, possibly because the local diet may have altered or readjusted the intestinal flora and thereby encouraged competition for essential substances Protein deficiency *per se* does not appear to be a direct aetiological factor Protein administration alone will not cure these anaemias; specific haemopoietic treatment must be given There is an association between pregnancy and the appearance of megaloblastic anaemias, but they also appear in non-pregnant women and in men They may complicate the picture in tropical sprue, especially in certain geographical areas in the Americas Infection with *Diphyllobothrium* tape worms may initiate similar blood changes

Normoblastic macrocytic anaemias are usually of secondary origin in that the disorder is not primarily localized to the blood forming system, i e there is no megaloblastic erythropoiesis Scurvy and myxoedema may produce this blood picture which also occasionally

The relapse may be quite as severe as the original episode, the same syndrome is produced, including the depigmentation of the hair, the colour and texture of which is restored during treatment and recovery; in this way the growing hair may exhibit alternating bands of normal black pigmentation and grey or red depigmentation, the so called 'flag sign'

Parasitic and bacterial infections must be treated. Some authors recommend a blanket treatment with penicillin for the first few days in all severe cases In hyperendemic malarial areas a course of chloroquine is similarly recommended. Others prefer to control the nutritional defect before attending to the infections, unless the latter are obvious and severe. In general the control of helminthic infections should be left until convalescence.

Specific vitamins may do more harm than good and lipotrophic factors such as methionine and choline are of no appreciable benefit

ANAEMIAS IN THE TROPICS

Anaemia results from excessive loss of blood, increased blood destruction, impaired erythrocyte formation or any combination of these mechanisms Efficient correction of an anaemia depends on the discovery of the pathological processes causing it. In the tropics, unfortunately, there are often many aetiological factors in a single individual case Of these, certain parasitic and helminthic infections and hereditary haemoglobin abnormalities may be readily detectable. Many of the other factors are obscure, as is indicated by present multiplicity of classifications of so-called 'tropical' anaemias.

Hypochromic anaemias met in the tropics may be either normocytic or microcytic Of these, one large group responds to iron therapy and is regarded as iron-deficient The others do not

Amongst the iron-deficient group are those arising from dietary iron deficiencies and those associated with chronic blood loss In the latter group are the relatively rare anaemias of heavy hook-worm infection; the hookworm loads commonly met do not *per se* lead to anaemia Other causes of bleeding, such as duodenal ulcer or scurvy may also cause anaemia. A single specific aetiological factor is unusual, however, in the ordinary run of iron-deficient anaemias, which occur commonly in pregnant women, but also in non-pregnant women and in men Dietary iron deficiency is rare in the tropics, where the intake is usually

able synthesis by gut bacteria Nutritional anaemias are sometimes refractory to B_{12} therapy, and the same is true of the anaemias due to intestinal disease

Vegetarianism A macrocytic hypochromic anaemia is not uncommon in vegetarians At first this was thought to be due to lack of protein, but more recent work has shown that there is a substance present in meat which is known as the 'animal protein factor' It may possibly be identical with vitamin B_{12}.

Other factors It is highly probable that there are other substances present in liver and yeast which are concerned with haemopoiesis They have not yet been isolated

[illegible]

conjugated folic acid Thus in pernicious anaemia there is an increased excretion of folic acid after administration of B_{12} Also both liver extract and B_{12} may fail to produce a haematological response in a dietary absence of folic acid this is especially true of the macrocytic anaemias of pregnancy and infancy

TREATMENT

The treatment of nutritional anaemias is largely empirical The simplest and cheapest forms of treatment should be tried first, unless the patient is definitely ill, in which case folic acid should be given and then, failing a response, vitamin B_{12} or liver extract The treatment routine suggested is

1 Examine for and, if present, treat such infections as ancylostomiasis

2 Adjust the diet, so far as possible, to the ideal If meat is precluded, yeast 1-4 ounces daily should be taken Green vegetables and salads are advisable spinach contains much folic acid Added iron, preferably ferrous sulphate 5 grains daily by mouth, may be necessary for a few weeks

These two steps alone will usually be successful

3 Folic acid by mouth The initial dosage should be 10 mg twice a day for about 10 days after this the amount can be reduced to 5 mg or 10 mg daily.

4 Vitamin or liver extract by injection A maximal bone marrow response is usually obtained with 10 µg of B_{12} 20 to 50 µg per week should be sufficient for maintenance The amount of liver extract used depends on the preparation crude extracts may be highly active

If the anaemia requires prolonged vitamin therapy it is not nutritional in origin, and some other cause should be sought

develops in chronic hepatic dysfunction and cirrhosis associated with hypersplenism. Many erythrocytes will be found to be considerably above normal size; they are extremely thin and may even be hypochromic

The aetiology of anaemia in the tropics is confused by the social life of the people, by vegetarianism, by malnutrition and by protozoal and helminthic diseases. The diagnosis of the cause in a given case is often extremely difficult. It requires care and patience, a knowledge of the living conditions of the individual concerned and of his parasitological and infective background It also demands a common sense regard for the fact that most of the ordinary causes of anaemia in temperate climates may also be operative in the tropics.

TROPICAL NUTRITIONAL ANAEMIA

Nutritional anaemias are usually complicated by co-existing disease, the converse also being true. Anaemias are therefore commonly a product of both disease and malnutrition, though this is not invariably so

All the factors necessary for the production of normal erythropoiesis are not known, and several substances have yet to be isolated.

Disease: Many diseases occurring in the tropics give rise to anaemia Most of these anaemias are either normocytic or microcytic, unless there is co-existing deficiency in which case macrocytosis may be present. Macrocytosis may accompany intestinal disease, when a stricture or blind intestinal loop gives rise to stagnation of intestinal contents certain diseases of the bowel may, however, give rise to a microcytic anaemia, diarrhoea, as in sprue, may be associated with macrocytosis

Iron deficiency Uncomplicated iron deficiency gives rise to a microcytic, hypochromic anaemia When there is also insufficient folic acid in the diet the picture may change to macrocytosis. Chronic haemorrhage, e g ancylostomiasis, may lead to iron deficiency on an apparently adequate diet.

Folic acid: Nearly all macrocytic anaemias respond to folic acid, and it is possible that most tropical nutritional anaemias and the macrocytic anaemias of pregnancy and of infancy are, at least in part, due to folic acid deficiency The folic acid content of milk, especially goats' milk, is low, and 'goats' milk anaemia' is probably due to lack of the vitamin.

Vitamin B_{12} An inability to absorb B_{12} from the gut is the essential feature of pernicious anaemia, but it is doubtful whether a dietary lack, unaccompanied by defect in absorption, can arise owing to consider-

clinical features comprise vomiting of abrupt onset, followed by prostration, drowsiness, coma and sometimes death There is no associated pain, fever, diarrhoea, or other malaise Recovery, if it occurs, is usually complete within 42-72 hours During the illness, blood sugar levels are extremely low – perhaps as low as 10 mg per cent, and intravenous therapy with 50 per cent glucose solution should not be delayed

It is thought that vomiting and hypoglycaemia are the effects of a toxin temporarily blocking gluconeogenesis in under-fed children whose reserves are not great A possible source of such a toxin is the Ackee plant, an important element of Jamaican diet Polypeptides isolated from unripe Ackee have shown hypoglycaemic activity in laboratory animals A similar syndrome of vomiting and hypoglycaemia occurs in America following ingestion of White Snake Root

Hepatic veno-occlusive disease also occurs in Jamaica and has been reported from Israel and India In Jamaica, children 1-3 years of age and of poor families, are acutely affected This acute stage often follows an illness such as respiratory infection, and features are loss of weight, enlargement of the liver, ascites, and pressure oedema of the legs Those who survive the acute stage may in later childhood show evidence of hepatic cirrhosis with hepato-splenomegaly, portal hypertension and ascites

The pathogenesis of the syndrome is uncertain, but intrahepatic blockage of the hepatic venous system, by spasm of small veins or by sub-endothelial oedema, is known to occur It is thought that these changes may result from ingestion of toxic alkaloids in 'bush tea'

NUTRITIONAL OEDEMA

The oedema which occurs frequently in the undernourished is due to more than one factor

An insufficient amount of dietary protein may lead to a diminished concentration of plasma albumen, especially when on a diet of a very low caloric value If the concentration of plasma albumen falls to about 2 5 gm per cent or lower oedema usually develops, owing to the low osmotic pressure within the blood. Thiamine deficiency may produce acute cardiac failure, with oedema and ascites; it is probable that the *deficiency also increases peripheral capillary permeability*. A diminished diuresis also occurs in the undernourished, the reason for which is obscure and rest in bed frequently increases the urinary output.

The oedema of beriberi has usually a threefold origin, namely a low plasma albumen concentration, cardiac insufficiency and increased capillary permeability The origin of famine and hunger oedema varies, and the factors mentioned above may each act in a different degree according to the dietary circumstances

No rigid rule for treatment can be given. *Nutritional oedema is* almost invariably accompanied by signs and symptoms of another deficiency syndrome, such as kwashiorkor Treatment of the accompanying syndrome usually cures the oedema also. In the absence of signs of vitamin deficiencies, the patient should be treated as for kwashiorkor, but thiamine 40 mg by mouth daily for 2-3 days may be added Children should receive half this amount

ENDOGENOUS FOOD POISONS

Epidemic Dropsy see page 64

Lathyrism an acute spastic paralysis of sudden onset, associated with weakness, muscular pains, and sometimes incontinence of urine, is a syndrome which has been reported from many countries, and particularly India, Iran, Africa and the Mediterranean littoral It occurs among poor people who eat lathyrus peas, and has its highest incidence late in the season when the crop has been stored for some time, and also during droughts and famines when malnutrition is rife and the

predominantly in young children of Jamaican peasants The usual

The blood Wassermann and similar reactions are negative in the early stages of pinta, becoming positive in most cases after some months The reactions are positive in the majority of long-standing cases They are sometimes positive in the spinal fluid, but it is not certain whether such changes arise from the pinta itself or concomitant syphilis In some geographical regions pinta and yaws are coincidental The two diseases sometimes appear contemporaneously in the same individual

CLINICAL PICTURE

The lesions occur on the skin, and only rarely on mucous membranes In the early stages there are no constitutional symptoms Primary lesions are believed to appear at the point of infection In experimental infections they develop in 1 to 8 weeks, commencing as intensely itching slightly raised erythematous papules which spread slowly, often developing small satellite papules In the course of some months a raised infiltrated plaque is formed, sharply demarcated and covered with laminar scales In dark skinned individuals the lesion is slatey grey or even blue The plaque slowly spreads, becoming ovoid or irregular in outline as the satellite lesions are absorbed into it

For a long time the primary lesion may be the only one present Eventually, after 4 to 12 months, other lesions appear, indicating some general spread of the infection These later lesions, or 'pintids', develop in much the same way as the primary, starting as small papules, and developing into plaques with actively growing edges which tend to become confluent Large irregular areas of skin may become involved

The plaq[illegible]

[illegible]

[illegible]

epithelium Accumulation of pigment in the corium may give a bluish or blackish tinge to the lesions which stand out against the surrounding skin

Pintids may be few and confined to the extremities, or multiple involving most of the trunk and limbs They appear successively during the secondary stage, so that lesions in all stages of development may be present at any one time in the same patient

The initial lesion usually persists during the development of pintids In some cases lesions may undergo spontaneous recession In others the dermal development may be continuous and uninterrupted Sometimes the disease subsides completely, becoming latent and remaining so for years, eventually reappearing as cutaneous lesions commonly in the extremities

Pintids are painless, but may be very itchy and become secondarily infected Moderate local glandular enlargement is common

XXI

PINTA

DEFINITION

A CONDITION caused by *Treponema carateum* closely resembling yaws, resulting in skin lesions.

DISTRIBUTION

Pinta is found in rural areas in Central and South America, including Mexico, British Honduras, Venezuela, Colombia, Peru, Brazil and Ecuador, and in the Carribean Islands, especially Cuba

AETIOLOGY

The causative agent is *Treponema carateum* which is morphologically indistinguishable from *T pertenue*

Lesions are rare in children under the age of one year. The infection is acquired most commonly in childhood or adolescence. Both sexes are involved equally. Pinta is most probably transmitted by contact in a similar way to yaws It is possible that non-biting flies may sometimes be involved Like yaws, pinta is found most commonly in dark skinned populations and rarely in Europeans, probably because the insanitary conditions under which the former live promote transmission.

Pinta produces a much weaker cross immunity with syphilis than does yaws, coincident infection with syphilis apparently is relatively common Superinfection is possible during the early stages while the lesions are developing

PATHOLOGY

The basic lesion is a slowly developing subcutaneous granulomatous reaction, together with hypertrophy and eventual atrophy of the overlying skin and various colour changes produced by re-distribution of dermal pigment In early lesions pigment is lost from the germinal layers of the epithelium and may become concentrated and widely diffused in the upper layers of the corium In the later stages there may be complete depigmentation of epithelium and corium

Lymph glands draining the areas of skin involved may be enlarged and show a mild granulomatous reaction and characteristic accumulation of melanin throughout the tissues.

Visceral lesions, including changes in the heart and large vessels and changes in the spinal fluid have been described but have not been clearly differentiated from syphilis.

XXII

PLAGUE

DEFINITION

A WIDESPREAD, often fatal, bacterial disease, caused by *Pasteurella pestis*, a primarily rodent infection, which is spread to man either by the bite of an infected rodent flea in the case of bubonic plague, or by droplet infection in the case of pneumonic plague

Plague usually occurs sporadically or in epidemic proportions in congested urban areas as a result of transmission of infection by the fleas of domesticated rats It may also occur in sparsely populated districts amongst those who come into contact with wild rodents which harbour the infection (sylvatic plague)

The clinical course is rapid and the mortality high

DISTRIBUTION

Plague is endemic in parts of northern, western and central India It appears sporadically in many other tropical and subtropical countries including Iraq, Iran, Siam, Burma, southern China, Indo-China, Ceylon, the East Indies, Africa, including Morocco, Senegal, the Congo, Kenya and Uganda, parts of South America, Madagascar Occasionally cases are reported in western European ports

Sylvatic plague occurs, sometimes with associated pneumonic outbreaks, in south-east Russia, Mongolia, Manchuria, the Transvaal, Orange Free State, Brazil, Argentina, Peru, Ecuador and parts of the western United States

AETIOLOGY

CAUSATIVE ORGANISM

[illegible]

moist conditions and sometimes for weeks in flea faeces It survives freezing for longer periods

Permanent immunity is usually conferred by an attack of plague Second attacks have occasionally been reported

s

In the late stages the initial lesion and pintids eventually become depigmented and the skin over them smoothed and atrophic. They remain slightly erythematous and continue to grow. Other depigmented atrophic lightly erythematous areas may appear which fuse to

ally the dorsal surface of the hands and forearms, the wrists and the heels The lesions are commonly arranged symmetrically. Those in the wrists are often disposed in roughly triangular areas with the apex pointing up the arm

The late lesions comprise a superficial achromic dermatitis scattered over a dark background The skin over the depigmented areas may be normal, in which case the area is often ringed with dark pigment. More commonly it is atrophic, smooth or slightly desquamated.

In the palmar and plantar regions there is often diffuse or scattered loss of pigment, sometimes with irregular spots of hyperpigmentation The skin surface may be unchanged or atrophic and desquamating In some cases there is notable palmar and plantar hyperkeratosis, occasionally with contractures, conical depressions in the horny layer, and fissuring, presenting a picture very closely resembling that of yaws. Some authorities, indeed, regard these advanced lesions as yaws

DIAGNOSIS

The geographical distribution of the disease is important. The slowly growing lesions and changes in pigmentation, especially the white atrophied lesions of the tertiary stage, are characteristic. Many other conditions, including yaws and certain fungus infections, for example, *Tinea versicolor*, may produce irregular scattered depigmentation of the skin, but these changes are seldom symmetrical Piebald

the epidermis in primary lesions and pintids. They may also be present in late lesion in the rete mucosum

TREATMENT

Penicillin, administered as in yaws, is successful in the early stages

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as little

render

it negative in early cases

disease remains as an enzootic in the reservoir animals When it becomes an epizootic and other conditions are suitable, the disease eventually appears in man in epidemic proportions The epizootic precedes (usually by about a fortnight) the epidemic and is commonly indicated by a high rodent mortality When the rat population has been suitably reduced, the epidemic spread stops The pattern of an uncontrolled epidemic of plague is thus a slow beginning, a very rapid rise (as the epizootic develops to the full) and an equally abrupt fall after some months

Spread from district to district may occur as the result of extension of an existing enzootic or epizootic

Sporadic cases may result in some districts from migration of infected rats, particularly in ships, without the involvement of the local rodent population Plague has sometimes been spread by the carriage of infected fleas in merchandise and clothing

Ambulatory cases may carry the disease to new areas and lead to infection of local rodents

THE SPREAD OF SYLVATIC PLAGUE

Plague persists in certain sparsely populated or rural districts as an enzootic in wild rodents In these districts it appears sporadically in man, especially amongst people whose work brings them into contact with the reservoir animals Occasionally it appears in epidemic proportions

The enzootic is kept going by flea transmission from rodent to rodent Man may acquire the infection by dissecting or skinning infected wild animals or being bitten by their fleas

Epidemics occasionally arise as in urban plague when semi-domestic rats become infected after contact with wild rodents and convey the infection via fleas to domestic rats This usually happens during an epizootic amongst the reservoir animals, but epizootics probably often occur without epidemic spread

Unlike the domestic rat, wild rodents may migrate considerable distances and carry plague with them, infecting fresh rodents in new localities In this way the disease may appear sporadically over very wide areas

FACTORS INFLUENCING THE SPREAD OF PLAGUE

Once the domestic rat has become infected, plague will spread rapidly wherever the human population is congested and living in insanitary conditions in which rats abound and have easy access to food

The flea population is very sensitive to climatic conditions and since only relatively few fleas on any given rat become capable of

TRANSMISSION

Plague is naturally an enzootic in a wide group of rodents. It is normally transmitted from rodent to rodent by fleas

Man may be infected in two ways (i) through the infected flea (or occasionally the louse or the bed bug), and (ii) through droplet infection spreading from cases of pneumonic plague.

(I) TRANSMISSION BY THE FLEA

The common vectors Human plague depends for transmission principally upon rat fleas, of which *Xenopsylla cheopis* is the most efficient vector and *X brasiliensis* and *X astia* much less efficient The human flea *Pulex irritans* is difficult to infect with *P pestis* but may occasionally be concerned in transmission The fleas of cats and dogs and of the rodent reservoirs of sylvatic plague do not readily bite man, but may transmit infection if biting occurs

The mechanism of infection through the flea Plague bacilli may be passed in the flea faeces and rubbed into the tissues through skin abrasions or the flea bite They may also be carried directly on the mouth parts of the flea after previous biting of an infective source By far the commonest mode of spread, however, depends on the blocking of the proventriculus of the infected flea by rapidly multiplying bacteria The blocking makes ingestion of blood impossible and the flea becomes hungry and tries repeatedly to feed Its efforts are rewarded only by regurgitation of blood and bacteria In this way a single flea, although

Survival is longest in a relatively cool moist environment Hot dry conditions are rapidly fatal

Unblocked infected fleas do not usually survive for longer than a fortnight Under suitable circumstances (for example, in rat nests), they may remain alive for months and so carry the infection over from one season to another

Plague exists in two main epidemiological forms, urban and sylvatic The mechanics of transmission differ somewhat in these two forms but the basic factors are essentially the same

THE SPREAD OF URBAN PLAGUE

Plague existing as an enzootic in wild rodents is accidentally transmitted to the semi-domesticated brown rat *Rattus norvegicus* The latter dies and *infected fleas leave it and migrate to and infect the domestic rat, Rattus rattus* When this in turn dies (in the course of a few days) the infected fleas feed on man and plague appears

Sporadic cases occur from time to time in this manner so long as the

enlarge, become congested and may contain scattered areas of focal necrosis and haemorrhage.

The heart muscle is frequently involved, the tissue becoming oedematous, haemorrhagic and infiltrated with inflammatory cells A haemorrhagic pericardial effusion commonly develops

The lungs may be seriously involved There may be acute oedema, congestion and haemorrhage into alveoli and small bronchioles, and patches of haemorrhagic consolidation which may coalesce to involve

pneumonic plague similar pulmonary lesions develop as the result of inhalation of infective droplets A bacterial bronchiolitis and alveolitis is set up and extends to become bronchopneumonia and finally lobular consolidation The bacilli multiply locally in enormous numbers leading to early and severe toxaemia and bacteriaemia The pulmonary lymph glands and contiguous tissues become involved within a few hours, the lesions resemble those of the characteristic bubo but are less intense Lesions in other organs may appear, similar to those seen in bubonic plague, but death may occur so quickly that these may not develop

Early prostration, stupor and delirium indicate involvement of the central nervous system, but necropsy does not always reveal concomitant physical damage to the brain, which is, however, usually congested and often spotted with petechial haemorrhages The cerebrospinal fluid may be turbid – containing many neutrophils Occasionally there may be a frank *Pasteurella* meningitis, which rarely occurs as a primary lesion

CLINICAL PICTURE

The clinical pattern of plague varies A few cases may be so mild as to pass practically unnoticed There may be merely a small vesicle and light inflammatory reaction at the site of the infected bite, with no constitutional disturbance at all, there may be some local adenitis which persists without general symptoms for a few days or weeks before

transmitting the infection, factors which limit the number of fleas are often important in determining the spread of the infection in man.

In temperate climates the disease is commoner in summer and autumn, when the fleas are most numerous In the tropics it appears mostly in the cooler weather or during periods of high humidity.

[illegible]

ar [illegible] several seasons, the incidence in the following year is likely to be low

Spread to man depends very largely on the closeness of the association of semi-domesticated and domesticated rats once the former are infected In areas in which the domesticated rat has been largely ousted by the less domesticated brown rat, the spread of plague is considerably reduced, and may practically cease

(ii) DROPLET INFECTION

It is probable that the original spread of pneumonic plague occurs from a patient infected in the ordinary way by the flea and in whom pulmonary complications have developed Once established, pneumonic plague spreads from subject to subject by droplet infection. Cold or freezing conditions with relatively high humidity favour droplet spread Further spread is facilitated by congestion of population and intimate contact between healthy and infected subjects

PATHOLOGY

The pathology of plague is non-specific. There is a vigorous but usually unsuccessful inflammatory reaction to the organism, which is accompanied by varying degrees of toxic tissue damage especially to the endothelial lining of the lymphatics and blood vessels

In bubonic plague there may be a local lesion at the site of infection, appearing first as a vesicle, later becoming a focus of necrotic inflammation

The bubo forms in the lymph glands draining the point of infection These glands enlarge rapidly and become matted together in oedematous haemorrhagic connective tissue and may ultimately suppurate The changes in the glands are essentially inflammatory. The blood vessels are intensely congested; there may be haemorrhages into the substance; there is a massive cellular inflammatory infiltration Small necrotic foci form and may coalesce to become abscesses eventually discharging to the surface The affected glands contain enormous numbers of bacilli In most cases the infection probably reaches the blood stream, and all organs may become involved. There is generalized vasodilatation, notably in the liver and spleen, both of which

As the condition progresses the mental dullness often gives way to anxiety and restlessness and the patient may become highly excited and even maniacal On the other hand, the lethargy may deepen and coma eventually develop

The Bubo Extreme local pain and tenderness at the site of the developing bubo are commonly present from the onset, even before the swelling appears In most cases the bubo appears on the second day after the onset of fever In some it may be the first sign of illness It takes 2 to 5 days to reach full size The affected gland or glands are at first hard and painful and swell rapidly Their position depends on the site of infection In over 70 per cent of cases the bite is on the leg and the groin glands are involved; the axillary glands are affected in about 20 per cent The bubo is very painful and tender The skin over it is erythematous and hot, the surrounding subcutaneous tissues are oedematous and sometimes haemorrhagic Because of the pain the patient adopts a characteristic attitude in an attempt at relief When the bubo is in the groin he lies on the other side, with the knee flexed and the thigh drawn up, when it is in the axilla the arm is abducted and extended

The [illegible]

Secondary infection is almost inevitable and chronic indolent ulcers or sinuses are often left after otherwise complete recovery Occasionally large vessels may be eroded and lead to severe haemorrhage After recovery from plague the patient may die from the results of the local sepsis

COURSE AND PROGNOSIS

The course of bubonic plague is short Without treatment from 30 to 90 per cent of cases die in an average outbreak Most deaths occur before the fifth day The outcome depends to a large extent on whether septicaemia develops Such a complication is indicated by a general worsening of the condition and often by a generalized moderate lymphadenitis A sudden fall of temperature about the time the bubo matures is regarded as a bad prognostic sign In many patients there appear to be irregular bursts of septicaemia, but once the local lymphatic barrier has been passed serious lesions may develop particularly in the liver and heart

SEPTICAEMIA

Septicaemia is always present in pneumonic plague and often late in the more serious cases of bubonic It is sometimes regarded as the primary syndrome, particularly when the infection has entered through the mouth In such cases death occurs within 1 to 3 days, before bubonic

that in practically all cases bacteriaemia without multiplication of the organisms occurs as a transitory phenomenon, reappearing later in appropriate context as a true septicaemia, with massive multiplication of the organisms So-called 'primary septicaemia' cases are probably examples of this secondary bacteriaemia in which deep-seated buboes have been overlooked or in which the gland reaction has been inconspicuous

BUBONIC PLAGUE

The majority of cases develop a bubo in the regional lymph glands draining to the area infected There is commonly only one bubo, but there may occasionally be more.

The incubation period ranges from 2 to 10 days; the commonest period is 3 to 4 days. Prodromal symptoms consist of headache, backache, malaise and apathy.

The onset is sudden, with a moderately severe rigor or a series of shivering attacks There may be convulsions in children In the course of the first day the temperature rises to 103° to 104° F or higher The temperature remains elevated and remittent for the next 2 to 5 days and then falls slowly or suddenly, the fall of temperature usually corresponding to the full development of the bubo Suppuration and secondary infection of the latter causes a later return of fever

The general appearance of the patient is characteristic. In the early stages he lies dull and apathetic He is confused and may complain of severe backache, and headache The overall appearance is one of advancing stupor and prostration The speech may be slurred, there may be muscular tremor and twitching and the gait may be unsteady.

The skin is hot and dry There is general blotchy vasodilation, especially notable in the face. The conjunctivae are congested. There may be petechial haemorrhages in the skin Large or small subcutaneous haemorrhages may be prominent in some outbreaks Occasionally patches of skin may become necrotic.

The tongue is dry and sometimes swollen. The surface may become covered with a dark grey or black coating Sordes is common.

The pulse in the febrile stage is fast It may become almost uncountable in the late stages

In severe cases the heart dilates and death may result from cardiac failure The blood pressures are often low and vascular failure may supervene terminally, in which case the diastolic pressure may be unmeasurable The respiratory rate is fast at the onset and may increase as the disease develops. There may be some epigastric pain, nausea and sometimes vomiting

The spleen is moderately enlarged and tender. There is usually some polymorphonuclear leucocytosis

regarded as a possibility in cases of adenitis in an endemic area The sudden onset with high fever, prostration and toxaemia especially affecting the central nervous system and heart are suggestive Before establishment of the bubo, or in primary septicaemic cases, diagnosis may be very difficult, and confusion may arise especially with typhus

In mild cases the bubo may be mistaken for lymphogranuloma or other forms of adenitis Bacteriological examination of the gland juice should settle the diagnosis

In primary pneumonic plague the diagnosis should be confirmed by examination of the sputum which swarms with *P pestis*

Rapid if tentative diagnosis may be possible by identification of characteristic pleomorphic bipolar organisms in smears (stained with Gram) of juice from the bubo in its early stages In septicaemic cases the bacilli may sometimes be numerous enough to show in a blood film Pus from more advanced buboes may not show *P pestis* clearly

Laboratory aids to diagnosis may be a great help in so far as the community is concerned, but because of the time necessary to carry them out, may be of little value to the individual case

The examination of dead or trapped rats is nevertheless most important in the diagnosis of plague The animal to be examined should first be immersed in disinfectant solution in order to destroy its ectoparasites The post-mortem changes of plague are characteristic There is diffuse intense subcutaneous congestion and ecchymosis Lymphatic glands, particularly those in the neck and groin, are usually enlarged and necrotic The serous cavities may contain blood-stained fluid The liver is large, pale and peppered with small greyish necrotic areas The spleen is large, deeply congested and may show scattered small necrotic foci The lungs are congested, oedematous and may contain similar foci

All organs are teeming with organisms which are easily seen in smears stained by Gram's method

Bacteriological confirmation of the nature of the organism is necessary to distinguish it from *P pseudo-tuberculosis* This can be had in a few days by bacteriological culture, by rubbing the suspected material on to the shaved belly of a guinea pig or by subcutaneous inoculation of a suspension of ground up fleas from a suspected rat The animal will die in 3 to 5 days if plague is present The autopsy picture is similar to that seen in rats dead of plague

Bacteriological investigation should be undertaken only under insect-proof laboratory conditions

TREATMENT

The patient should be nursed in bed Good nursing is a very important part of treatment, especially if the heart is involved. Exertion

or pneumonic evidence of infection can fully develop The onset is sudden with rigor and high fever and severe headache. The patient is prostrated. Restless and anxious at first, he becomes delirious and soon stuporose or comatose Signs of heart involvement develop quickly and the pulse becomes very fast There may be severe haemorrhage into the gastrointestinal tract, or from visible mucous membranes

PNEUMONIC PLAGUE

In the terminal stages of bubonic plague, pulmonary complications may appear which are similar to those described below. The term pneumonic plague, however, is usually reserved for those cases in which the pneumonic involvement originates from the inhalation of infective material and in which the lung is the primary site of invasion

The onset occurs abruptly two or three days after exposure Prodromata are rare Rigor is usually absent but there may be early chilly feelings and some shivering The patient complains at first of headache, backache and anorexia The temperature rises to 103° or 104° F or higher in the first 24 hours, after which clinical signs of pulmonary involvement appear A frequent and initially painless cough develops and the patient becomes increasingly dyspnoeic. The sputum is at first mucoid or watery and rapidly becomes tinged with blood and finally bright red or brown, frothy and loaded with plague bacilli Pain in the chest becomes severe and breathing more and more rapid and difficult, the patient gasping for breath as the pneumonic process develops Towards the end there is often considerable cyanosis The physical signs in the chest are equivocal; there may be fine râles at the bases, some dullness on percussion Signs of heart involvement are always early and severe. The heart dilates, the dullness extending to the right The blood pressures fall, the pulse rate quickens and may be almost uncountable Death occurs usually in 1 to 3 days, rarely longer.

Bacilli are present in the blood from the beginning, sometimes in relatively large numbers There is always a considerable polymorphonuclear leucocytosis with a white count of 40,000 cells or more per cu mm

Vascular damage is usually evident. Haemorrhages from the mucous membranes, epistaxis, haemoptysis, haematuria and widely scattered petechial or larger haemorrhages into the skin may occur

Without specific treatment pneumonic plague is almost invariably fatal Modern chemotherapeutic methods have greatly changed the outlook

DIAGNOSIS

The clinical diagnosis of bubonic plague is of great importance. It should be easy during a known outbreak and plague should always be

with and without sulphonamides There seems little indication for their continued use

CONTROL

The Case As far as possible sporadic cases of flea-borne plague should be isolated in hospital When cases are numerous, they may be successfully treated with sulphonamides or streptomycin in their own homes provided immediate measures against fleas and rats are instituted

Bodies of patients and rats should be handled with care by suitably clothed attendants (gowns, boots, gloves, masks and caps) and either burned or buried in quick-lime

Pneumonic cases must be isolated They should be attended by a minimal nursing and medical staff who must wear protective clothing and face masks

Overalls, gloves, masks and caps are advisable during the treatment of all plague cases DDT impregnated clothing reduces the risk of flea bite, since fleas cease to be active within 10 minutes of exposure to the insecticide

Contacts The other occupants of a dwelling in which flea-borne plague has occurred should be regarded as contacts exposed to infective flea bite They should be given chemoprophylactic treatment as below, and watched for clinical signs

All those who have been exposed to a case of pneumonic plague are regarded as contacts in considerable risk to themselves and their associates It has been the practice to isolate them separately if possible or otherwise in groups, and watch them for at least a week, removing for further strict isolation and treatment any who show signs of illness

Recent successful prophylaxis of contacts with sulphonamides indicate that such antisocial measures are not necessary and that chemoprophylaxis alone may be sufficient

All those exposed to respiratory cases should be given either sulphadiazine or sulphamerazine in appropriate doses for adults and children Adult dosage regimes for sulphadiazine range from 6 gm daily for 3 days to 1 week after contact for intimate contacts, to 3 gm daily for the same period for others

Chemoprophylaxis is less efficient and more difficult to administer in respect to bubonic plague

Vaccination Some degree of personal protection may be obtained with dead or attenuated living vaccines of *P pestis* Single dose mass vaccination during epidemics probably lowers the attack rate Vaccinated individuals appear to respond better to chemotherapy than unvaccinated

Control of Rats and Vectors Flea control by all available methods including dusting infested areas with DDT, etc , should be carried out

should be avoided as far as possible until well into convalescence since myocardial inefficiency often persists for some time after the acute illness. The skin requires particular attention where petechial or subcutaneous haemorrhages are present.

Symptomatic treatment may include morphia for restlessness or local pain at the site of the bubo. Fomentation may considerably ease such pain and assist the pointing of an abscess Incision and drainage of the bubo is not advisable until pointing has occurred; such interference may initiate septicaemia

Chemotherapy is now very effective and has greatly reduced the mortality, even in pneumonic cases. The most effective drugs are streptomycin and certain of the sulphonamides, including sulphadiazine (which is usually regarded as the most effective), sulphamerazine and sulphathiazole Where streptomycin-resistant strains of *Pasteurella* have been reported, oral tetracycline antibiotics may be substituted. Antiplague serum has been used as an adjuvant to chemotherapy

Streptomycin may be used alone or in combination with sulphonamides. The combined treatment is most effective.

Various dosage regimes have been recommended, including the following

1 *Streptomycin* intramuscularly or subcutaneously
0 66 gm immediately
0 33 gm every 4 hours night and day until temperature has been normal for 24 hours Very severe cases may be given 0 66 gm 4-hourly until the temperature has been normal for 2 days
A total dose of 4 to 25 gm may be needed

2 *Sulphadiazine* orally
4 0 gm immediately
2 0 gm 4 hours later
1 0 gm every 4 hours until temperature has been normal for 2 days
(Some authors advise continuing with 0 5 gm every 4 hours for a further 10 days)

3 *Sulphamerazine*
2 5 gm in 50 ml 5 per cent glucose solution at 8-hourly intervals for 3 doses, followed by 2 further injections of 1 5 gm at 8-hourly intervals, and then by 1 0 gm orally every 8 hours.

4 *Combined treatment*
Streptomycin intramuscularly 0 25 gm to 1.0 gm every 4 hours until temperature normal
Sulphadiazine as above (2)

Immune sera for the treatment and prophylaxis of plague have been prepared with various *Pasteurella* antigens They have been used both

XXIII

RABIES

DEFINITION

RABIES, or hydrophobia, is a condition due to infection with the rabies virus The disease affects a wide variety of warm blooded animals and birds, but is primarily one of carnivores,

symptoms develop

GEOGRAPHICAL DISTRIBUTION

ized countries where the disease was once very prevalent it has now largely been eliminated by suitable measures, from others, such as Great Britain and Scandinavia, it has successfully been eradicated solely by physical control of the domestic dog population

AETIOLOGY

The virus The causal agent is a neurotropic virus which can be grown only in nerve tissue The virus particles are large, they measure

destroyed by many antiseptics, by heat, by sunlight and by ultraviolet irradiation, it withstands desiccation, especially when in the frozen state. The virus survives for many weeks at 4° C, particularly if there is some neutral serum in the diluent, and for many months at temperatures below freezing, when dried and stored *in vacuo* it survives for years In neutral glycerol at room temperatures it remains viable for weeks, and at 4° C for many months

Pasteur and his colleagues many years ago showed that the virus could be recovered from the brains of animals dying of rabies and that it could be maintained indefinitely by subinoculations on to the surface

immediately plague has appeared. This will check the spread of plague but not eradicate it

Rat control is essential and must be carried on continuously by poisoning, trapping, rat proofing, protection of food and improvement of sanitation Routine examination of rats for evidence of plague should be instituted in every likely endemic area.

In urban areas such control is manageable with trained personnel It is difficult in rural areas, for which mobile teams are sometimes prepared

have been maintained and investigated in laboratories throughout the world Though there are antigenic variations between them, these variations appear to be quantitative rather than qualitative

Reservoirs In highly developed and urbanized countries the domestic dog is the usual reservoir of rabies infection, in the less developed and more primitive regions rabies is primarily a disease of wild animals, and dogs there play a minor role in its maintenance and spread With the travels of man and his dogs rabies has comparatively recently been introduced to many previously uninfected parts of the world For example it has become established by this means in the continents of North and of South America Here at first enzootic in the domestic dog, it has spread to the wild animal populations which now form the main reservoirs of the infection in these regions, the same applies to South Africa

Bat rabies In Mexico, Central and South America a paralytic disease [illegible]

tion is conveyed by the blood-sucking vampire bats peculiar to these regions The bat, *Desmodus rotundus*, feeds nocturnally by incising the skin of recumbent and sleeping animals, including man, and lapping blood which escapes from the wound This paralytic form of rabies appeared in Trinidad, British West Indies, some years ago and many human beings were infected A feature of the outbreak was the freedom of the numerous uncontrolled pariah dogs in the island from involvement The outbreak apparently was due to the migration of infected bats from the mainland By suitable measures the disease was banished from the island, which is once again free from rabies A unique feature of the rabies infection in these bats was that a proportion of them could transmit the infection in their salivary secretion for months as symptomless carriers, some of them subsequently even became non-infectious without manifesting signs of illness Others, however, when infected showed the usual abnormalities in behaviour, such as flying by day and fighting, and subsequently died of the disease

Lately it has been found that rabies infection occurs also in other bats – fruit eating and insectivorous – in association with infected vampire bats Presumably it was transmitted to them by the rabid vampires, but these other bats also have attacked mammals as a result of their disease and infected them Still more recently many species of insectivorous bats in Florida have been shown to be rabid, some cases of rabidity in mammals have resulted from attack by them Infected bats of various species have also been found in Louisiana, Texas and others of the southern United States

of the brains of serial animals When first obtained from naturally infected animals inoculation caused symptoms to appear after very variable periods, these were commonly between 15 and 20 days, but might be as long as 60 days or as short as 8 days This virus they called 'street virus'.

Repeated serial subdural transmissions of a strain of 'street virus' in rabbits resulted in shortening of the incubation period to a fixed limit of 6 or 7 days. A strain which underwent this change was called 'fixed' virus; once fixed a virus remained so and did not revert to the 'street' type The virus when fixed becomes more prolific but less hardy; it is much less infective when introduced into tissues other than the central nervous system; it does not disseminate through the nerves readily; and it usually fails to infect dogs when inoculated subcutaneously. A fixed virus infection in the dog usually causes symptoms of paralysis; a street virus infection those of excitability All strains of street virus and of fixed virus are antigenically identical; animals immunized against one are resistant to infection with all strains of rabies virus. Fixed virus is of very low virulence to man

Strains of street virus in nature may vary in virulence; their virulence can be estimated by the rapidity with which they become fixed on serial subdural inoculations in animals The degree of virulence of street viruses may be typed as follows: The first type consists of strains with a very short initial incubation period which is not further shortened by subdural maintenance These are very exceptionally virulent strains which correspond to Pasteur's 'Virus de rue renforcé'. The second consists (*a*) of virulent strains in which the initial incubation period is fairly short, but it shortens further during subdural maintenance and the virus becomes fixed after 15 to 30 subpassages, and (*b*) of the predominant strains in which fixation occurs after about 50 subpassages. The third consists of strains of abnormally low virulence which can be fixed only after very prolonged subpassage, some cannot be fixed at all Strains of this last type are extremely rare; they may cause mild manifestations followed by recovery in such a susceptible animal as the dog

Strains of virus Agglutinin absorption tests, and a study of antigenic structure, suggest that all strains are of a common origin It is probable that the virus undergoes changes in virulence and infectivity when the mammalian host and the rapidity of transference of a strain are abnormal. Rapid passage increases the speed of multiplication of the virus in the brain, but usually diminishes its tendency to invade the salivary glands. Abnormally virulent strains of virus commonly cause a paralytic form of the disease with a diminished tendency of the infected animal to bite; this reduces the opportunity for their transmission Many named strains of rabies virus showing individual peculiarities

occurs soon after infection they may not be found The larger bodies contain basophilic nucleus-like granules Their presence is proof of a rabies infection, but their absence does not exclude it While in man these inclusion bodies are unlikely to be present in any condition other

have no inner structure, and are more irregular in outline, they are found in the thalamus and lentiform nuclei rather than in Ammon's horn Negri bodies are found in the brains of nearly all dogs allowed to die naturally of a street virus infection, they are usually seen in humans dying of rabies, they are only exceptionally found in animals dying of a fixed virus infection

CLINICAL PICTURE

Incubation The incubation period varies greatly, usually symptoms appear between the 5th and 8th week Large series of observations show the average incubation period following a bite on the head to be 27 days, one on the arm to be 32 days, and one on the leg, the most common site, to be 64 days It has been postulated that the incubation period for a normal type of virus is proportional to the distance of the infecting bite from the central nervous system This view now is not generally accepted, today it is thought that it is the amount of virus and the tissue into which it is introduced which govern the incubation period In the experimental disease the incubation period varies inversely with the amount of active virus inoculated, and it bears no direct relation to the site of the inoculation The short incubation period following bites on the head and face, or hands, is due to severe laceration occurring in well innervated regions, thus a large amount of virus enters the wound and gets into nerve tissues

Furious rabies The onset of rabies is sudden, there may be a prodromal period lasting 2 to 3 days with malaise, nausea, vomiting, a sore throat and slight fever The patient then complains of headache and insomnia, and very often of pain at the site of the infecting bite, this latter is the first symptom of diagnostic significance He soon becomes uneasy, restless and a prey to anxiety; the breathing is rapid, with sighing respirations He is well orientated and while his attention is fixed the speech is normal, then anxiety overcomes him and his speech comes in rushes; he recovers with a sigh and there is a period of calm The attacks quickly become more frequent, intense, and spasmodic, the pharynx, larynx and eventually the whole respiratory apparatus become involved in them, extremely painful spasms are precipitated by attempts to eat or drink, and the patient becomes

Infectivity Though the saliva of an animal suffering from rabies may be infective it does not follow that all bitten by the animal contract the disease. Many persons have been bitten in rapid succession by a single rabid dog, and only a few of them contracted the disease. Statistics show that of some thousands of persons bitten by subsequently proven rabid animals, and unprotected by vaccine treatment, only 5 to 15 per cent contracted rabies.

PATHOLOGY

Infection and spread The virus as a rule is introduced into a wound or abrasion of the skin contaminated by the saliva of an animal suffering from the disease It enters the small nerves in the immediate vicinity and by diffusion or multiplication spreads along the nerves and up the appropriate nerve trunks, a process called 'septinèvrite'. The infection ascends the peripheral nerve trunk to the spinal cord and brain, where it diffuses in the central nervous system and it spreads centrifugally down the nerves from it to nerve terminals and ganglia in various organs If those organs are secretory their secretions may be infective when infected ganglion cells are shed into them; this would explain the infectivity of saliva

may be small haemorrhages throughout the central nervous system. On histological examination there is some perivascular infiltration,

and vacuolated, their nuclei are eccentric, and the affected cells disintegrate The extent of these changes varies greatly; in cases of

In man they are most numerous in Ammon's horn, the cerebrum, bulb and cord, they may also be seen in endoneurocytes in the sensory fibres of the trigeminal and the sympathetic nerves of the face In dogs the hippocampus is the classical site in which to seek them, but they occur elsewhere in the brain and in the ganglionic nerve cells of the body

Negri bodies are rounded oxyphil bodies which stain readily with eosin, fuchsin, Giemsa's stain, iron-alum-haematoxylin, and various special stains. They range in size from 0·25 to 25μ; the longer the duration of the disease before death the larger they are When death

mouth anything within reach during the spasm, and of the stomach type, with a spasm of the abdominal muscles often induced by attempts to eat or drink These spasms end with a violent respiratory effort and [illegible]

respiration rate, and the animal dies The tendency to bite persists right up to death Not all of these symptoms are evident at any one time, but most of them will be noted if the animal is closely watched over some days The saliva of the dog may be infective for a few days before clinical signs appear and remain infective until death In some dogs with furious rabies the virus does not appear in the saliva, which therefore is not infective

At autopsy the gross findings are not distinctive There may be haemorrhages and small erosions of the gums; there are usually dried scabs of mucus obstructing the nasal orifices, the peritoneal and mucous coats of the stomach are often congested, and there is often a variety of indigestible bodies in the stomach The head of the dog should be removed, packed in ice, and sent to a laboratory, alternatively, the skull may be split and the whole head be sent immersed in formalin solution The pathological changes in the brain, meninges and cord resemble those already described, the presence of Negri bodies proves that the animal suffered from rabies, their absence does not discount the diagnosis, which must be reviewed in relation to the other ascertained facts If the dog survived for more than 10 days from the onset of illness it is most unlikely that rabies was the cause of its death

TREATMENT

The site of the alleged bite must be examined at once, local treatment must be applied to it, inquiries must be set on foot into the circumstances of the occurrence, and arrangements must be made for the capture and detention of the offending dog

Rabies virus can only pass through a recent abrasion, it will not pass through an unbroken skin surface, and it will not penetrate granulations of more than 24 hours' duration The chances of infection increase in proportion to the extent of the laceration, deep punctures by teeth and some tearing of tissues are much more likely to result in a rapidly developing infection than are a few superficial lesions or minor abrasions Bites through clothing result in a reduction in the amount of infective saliva entering the wound

afraid to swallow. As the spasms intensify even the thought of drinking induces them, as do external stimuli such as sudden movement, a draught of air, a sound, or even a smell. A thick ropy mucus collects in the mouth and throat, and drips from the mouth between attempts to expectorate it. The voice is hoarse and raucous.

As the spasms become generalized convulsive seizures occur; during them the body is arched and rigid and the breath is held. There may be maniacal or 'furious' periods, particularly in manual workers of low intelligence, in which the patient throws himself about and destroys things within reach. During the intervals between the spasms the mind is clear. The reflexes are increased; palsies of groups of muscles may cause lack of expression, a squint, and inability to close the mouth or eyes; there is usually a rapid resting pulse rate, but sometimes bradycardia, and Cheyne-Stokes breathing is usual.

Death commonly takes place during a severe general spasm; but if [illegible] cease, [illegible] This [illegible] duration of the illness rarely exceeds 10 days in those infected from dogs, and commonly is no more than 4 to 5 days.

Paralytic rabies. Rarely the stage of excitement and spasm does not appear or is slight and ephemeral, and depression and progressive paralysis are the predominant manifestations. In such cases the onset usually appears as sudden weakness in an extremity; the usual difficulty in swallowing occurs only terminally. In the human cases of rabies following infection from bats in Trinidad, most primary infections were in the toes. There was an ascending paralysis associated with nerve root pains. An unusual feature of this outbreak was the survival of some of the patients for over two weeks, and in one case for thirty days, after the onset of the paralysis.

Rabies in the dog. Human rabies in practice is so closely connected [illegible]

tendency to hide; an altered appetite, shown by swallowing pieces [illegible]

delay The vaccine was prepared by emulsifying 1 cm of a selec
cord in 3 cc of saline; on the first day cords dried for 14 days were u:
then cords dried for progressively lesser periods were used, on the
few days of the treatment, which lasted about 18 days, 3 day cords w
injected on several occasions Pasteur thought that the desiccat
attenuated the virus, and that potentially more virulent virus
injected on each successive day of the course of treatment An ac
immunity was developed by the patient to rabies virus during
incubation period, and as a result his own infection was destro
before it reached the central nervous system The discovery that d:
cords could be stored in glycerin for considerable periods without
of antigenic potency much reduced the obvious difficulties of
Pasteurian treatment, as a result it became universally availabl

Since Pasteur's original vaccines prepared from spinal cords m
modified vaccines have been devised Rabies vaccines may broa

rabbit infected with fixed virus, he used it by injecting increasing c
centrations of from 1/10,000 to 1/250 over a period of a couple of we
Semple's was a prototype of a killed vaccine, he made a similar susp
sion of virus in infected rabbit brain, but added 1 per cent phenc
it and incubated it for one hour at 37° C to kill the virus Modificat
of both these types have followed, brain substance, which contai
greater concentration of virus than does spinal cord, has now aln
entirely supplanted the latter as a natural source of the virus Ki
virus vaccines became popular as they proved to be just as effecti
those containing living viruses The agents used to kill the virus h
been numerous Heat-treated vaccines and vaccines treated v
phenol, formalin, chloroform or ether, yatren, ultraviolet light,
many other chemical or physical applications have been develop

Though most patients treated with these vaccines suffer no ill-effe
in some cases complications have occurred About a week after the
dose of vaccine there may be erythema, oedema, pruritus, and pai
the site of the inoculation, these subside within a few days, though t
may recur in about ten days if the treatment is continued The reac

treatment is not stopped at once there may be graver manifestati

Local Local treatment of the wound is of great value, it has been shown that when thoroughly performed within a few hours of inoculation it materially reduces the risk of infection, though it does not entirely eliminate it Saliva must carefully be removed from the surrounding skin, without further contaminating the wound. Bleeding should be encouraged, where possible by the application of a ligature. The wound should be thoroughly cleansed, with a syringe, with a 20 per cent soap solution; every crevice and each tooth puncture must thoroughly be flushed. Caustic or necrotizing applications have been advocated for this purpose, such as the actual cautery, dilute or pure hydrochloric or fuming nitric acid, caustic soda, lunar caustic, or permanganate crystals; these are all very painful and cause subsequent disfigurement, none is superior to a simple soap solution if the wound is properly flushed with it soon after its infliction.

Excision of the wound may be considered; this if efficiently done is effective Excision or thorough cauterization with nitric, or hydrochloric, acid of the sites of experimental subcutaneous or intramuscular inoculation of rabies virus into guinea-pigs affords a high degree of sterilization if done even 24 hours after the injection In practice these more drastic, painful and mutilating procedures are no more effective than is the use of 20 per cent soap solution *if the local treatment is efficiently given within a few hours.*

The dog If the dog has already been destroyed, as is sometimes the case, the body should be procured for laboratory examination If living it should be segregated and watched for signs of the disease If the animal survives for more than 10 days it is not rabid; if it dies within this period the brain should be searched for Negri bodies. Late evidence that the dog is not rabid warrants the stoppage of treatment of the patient, but specific treatment should under no circumstances be delayed until such proof is forthcoming.

Specific There is no specific treatment for the disease once symptoms develop Two forms of preventive specific treatment are available during the incubation period These are (1) vaccine treatment and [illegible]

towards the end of the last century. He injected subcutaneously saline emulsions of the spinal cords of rabbits infected with fixed virus The freshly obtained cords before use were dried in the dark over sticks of caustic potash at a temperature not exceeding 22° C for periods ranging from 3 days to 2 weeks, these dried cords then had to be used without

The actual doses and methods of administration of rabies vaccine vary considerably with the vaccine used, and with the circumstances of the case In the case of a patient with severe lacerations the course of vaccine treatment of rabies is intensified Usually the vaccine treatment

The question of the need for retreatment of a patient not uncommonly arises If the time since treatment does not exceed three months further treatment is unnecessary unless a second exposure to infection is very severe If the interval does not exceed six months two reinforcing doses of vaccine, at an interval of a week suffice If it exceeds six months a full course of treatment should be repeated When allergy to the vaccine is manifested by a patient, the vaccine should be changed to one prepared from the brain of another species of animal or the Flury avianized strain if available may be used

Prophylaxis There must be rigid enforcement of quarantine regulations and control of the domestic dog population The prophylactic immunization of dogs, and of other animals at special risk, by vaccination is practicable and effective By this means rabies, which was periodically epizootic and endemic in Japan, has been reduced to negligible proportions The Flury-strain avianized vaccine given as a single injection appears to protect even dogs from a natural rabies infection for some years

in the form of encephalitis and paralyses. Peripheral neuritis, and an ascending myelitis with a Landry type of paralysis, may appear and sometimes end fatally, though in the majority of cases they eventually resolve without permanent after-effect. It is now considered that such complications are not due to the virus content of the vaccine, but to sensitization to the animal brain tissue from which it is prepared

Recently virus cultured in the living chick embryo has been used as a vaccine. Culture of street virus in this medium profoundly modifies the virus [illegible]
beec [illegible]
into [illegible]
injection of an 'avianized' living vaccine protects a dog against a street virus infection. No case of post-vaccinal paralysis in man has been known to follow its employment. A living 'avianized' strain of virus maintained solely in non-mammalian hosts since recovery from a girl dying of rabies is the basis of the Flury strain vaccine, which shows great promise both therapeutically and prophylactically. Peculiarities of this strain are that it is immunogenic only when given in the living state, and that it is more effective in this when given intramuscularly than subcutaneously. Its safety and value in the treatment of human rabies have yet to be fully established.

The standardization and comparison of the antigenic powers of rabies vaccines has for some time been difficult The Habel potency mouse test has been devised to solve the difficulty. A series of mice are injected intraperitoneally with a vaccine under test, and subsequently their immunity is challenged by injecting, intracerebrally, graduated dilutions of a standard fixed strain of virus into the protected mice By this means the protective potency of the vaccine is determined

Hyperimmune serum. A recent development in the treatment of rabies has been the development of hyperimmune sera These are obtained by actively immunizing large animals, such as sheep; taking large volumes of their serum; and concentrating the specific antibody in the serum The injection of this serum into a patient confers a temporary immunity The injection of a highly potent hyperimmune serum before active immunity can be developed by vaccine treatment may save the lives of those in whom the incubation period of rabies is abnormally short Serum used together with a vaccine offers the most effective means of preventing rabies after severe exposure to infection By this means the life of a child with intracranial punctures by the fangs of a rabid wolf was saved, together with the lives of others with grave injuries of the face and scalp In this series of cases greater and more speedy immunity, as judged by serological tests, was obtained by combined vaccine and hyperimmune serum treatment, than by the former alone.

break of human infection with *Strep moniliformis* has been shown to be the result of the consumption of unpasteurized milk containing it; the disease in this small epidemic in 1939 has been referred to as 'Haverhill Fever', from the locality where it occurred; a prominent feature of this outbreak was the high incidence of arthritis

It is now generally believed that *Sp minus* is responsible for one form of rat-bite fever Strains of the organism have been artificially maintained by serial subinoculation in animals, and in man for the treatment of general paralysis; in each case they caused the expected disease syndrome It is generally believed that *Strep moniliformis* is responsible for a second, but clinically very closely similar, form of rat-bite fever From human cases of this latter type the organisms can consistently be recovered by culture of the blood on suitable media Either of these two infections in man may result from the bite of a rat, but *Strep moniliformis* infection alternatively may be acquired by swallowing material containing the organism

Spirillum minus differs from the true spirochaetes in that its body is rigid, although it is motile its motility is due to terminal flagella It varies in length from 2 to 5 μ; the spirals, which are broad, number 2 to 4 or more The organism stains well with the Romanowsky stains or a silver impregnation method It is readily inoculable into laboratory animals, but it cannot be cultured *in vitro* The spirilla can be found widely in the organs of naturally infected rats, but not in the saliva It has been suggested that the infection following a rat bite is due to

been recovered from the lungs, in which it was held to be responsible for inflammatory and caseating lesions This organism may cause epizootics in mice, with involvement of the eyes, swelling of the lymphatic glands and of the joints, and paresis of the hind limbs

PATHOLOGY

The information available on the distinctive pathology of the rat-bite

enlarged, there is often a slight general lymphadenitis; and there may be arthritis with effusion In fatal cases the liver and kidneys show marked parenchymatous changes

XXIV

THE RAT-BITE FEVERS

DEFINITION

THE rat-bite fevers are considered to be due to infection with one or other of two distinct organisms, *Spirillum minus* and *Streptobacillus moniliformis*. Both organisms normally occur in rats and in a variety of other small animals. They gain entry to man not uncommonly as the result of a bite by a rat, and less frequently by that of another animal; the human cases of infection are incidental and sporadic. The clinical syndromes following infection with either organism are remarkably similar. They are characterized by a relapsing febrile illness of long duration, often with recurring inflammation of the bite-wound and local adenitis, and with an evanescent eruption, severe muscular pains and arthritis. The mortality is low.

GEOGRAPHICAL DISTRIBUTION

Cases of rat-bite fever due to either organism have been recorded from nearly every part of the world. Climate plays no direct part in their occurrence.

AETIOLOGY

For a great many years it has been appreciated that a febrile illness may follow the bite of a rat, and to a lesser extent that of many other small rodents and mammals. The identity of the causal agent of this illness has for long been confused and even now it is not beyond dispute. Early in the century filamentous structures, which have been diversely described and named, were recovered from cases of rat-bite fever. About 1916 Japanese workers reported the recovery of a spirillar organism from cases of rat-bite fever (sodoku) in Japan. This organism was named *Spirillum minus* and was accepted as the cause of rat-bite fever in man. After this recognition *Sp. minus* still could not be found in a proportion of the clinical cases of rat-bite fever, but reports of the presence of streptothrix-like organisms in these cases continued to accumulate. The names applied to these organisms were numerous and varied. After careful examination of the available literature, and a thorough study of further cases of rat-bite fever from which *Spirillum minus* could not be recovered, it is now believed that an entirely different organism causes a clinically similar disease. This organism is generally known by the name *Streptobacillus moniliformis*. Furthermore, an out-

organisms can be recovered from it by culture, spontaneous suppuration of the affected joints does not occur

The spleen and the lymph glands are said usually not to enlarge in cases of *Sp minus* infections, but commonly they do so in cases of *Strep moniliformis* infections Although both conditions are debilitating and may cause marked prostration, the mortality from either is low

DIAGNOSIS

Spirillum minus infections The organisms are not present in great numbers in the blood of man, even at the height of the fever, and it is rarely possible to find them in blood films They can be seen more readily in oedema fluid aspirated from the inflamed site of the infecting bite This fluid should be searched with dark ground illumination, or stained with Leishman or Giemsa, or by a modification of Fontana's silver impregnation method The most effective way of recovering and identifying the organisms is inoculation of the patient's blood, oedema fluid, or lymph gland puncture material, taken during a febrile period, into clean susceptible animals such as mice Some time may elapse before the infection becomes apparent in them, but the organisms can then be recovered from the blood, lymph gland juice, or peritoneal fluid of the infected animals *Sp minus* cannot be grown artificially in culture media

Streptobacillus moniliformis infections Laboratory animals normally are refractory to infection with this organism, but it can readily be cultured on beef infusion broth enriched wth rabbit serum Blood taken during a period of fever and sown on such a medium will yield a growth of the organism Agglutination tests may be performed with the patient's serum and a stock laboratory culture of the organism, and the organism isolated from the patient can be tested against a known agglutinating serum

TREATMENT

Spirillum minus infections These are very susceptible to treatment with arsenic Three intravenous injections each of 0 4 to 0 6 gm of neoarsphenamine at 3 day intervals usually suffice to effect a cure

Penicillin can be used as an alternative It has been stated that if a level of 0 05 units per ml of blood is maintained for 24 hours the infection is destroyed within that period This may entail a dosage of up to 1 million to 2 million units in divided doses in one day

Streptomycin, 1 gm daily for 10 days, has been stated effectively to eradicate the infection

CLINICAL PICTURE

The clinical manifestations due to the two types of rat-bite fever are very similar, and purely on clinical grounds it is impossible with reasonable certainty to differentiate them. The incubation period of the disease due to *Sp. minus* ranges from 5 to 30 days, the usual being about two weeks, that of the disease due to *Strep moniliformis* ranges *from 2 to 10 days, the usual being about 5 days* The bite causing the infection in either case appears to be healing, or to have healed, at the time of the onset of symptoms; in the case of the *Sp. minus* infection it then becomes inflamed once more and may develop a chancre-like ulceration with marked regional lymphangitis and lymphadenitis.

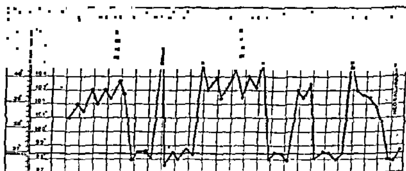


FIG. 40 Rat-bite fever Temperature chart of case of *Spirillum minus* infection [From E. Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

The onset of symptoms in either case is usually abrupt with a sharp rise of temperature, often of a remittent or septic type, and sometimes in association with shivering attacks In the case of *Sp minus infections* the fever lasts from 2 to 4 days, it then subsides and recurs after an

relapses In either infection an eruption commonly appears, this in the case of *Sp. minus* infections may be an evanescent bluish-red, or purplish, mottled erythema confined to the uppermost part of the trunk, or it may be maculo-papular and extend all over the trunk and limbs In the case of *Strep moniliformis infections the eruption is macular* and petechial in character In the case of *Sp minus* infections arthritis is unusual; but in that of *Strep. moniliformis* infections there is very commonly a polyarthritis with effusions into the joints, and this is a constant complication in those experimental animals successfully infected with this organism. The joint fluid contains many cells, and the causal

XXV

THE RELAPSING FEVERS

INTRODUCTION

THESE fevers are due to infection with strains of spirochaetes all of which morphologically are indistinguishable The infections are transmitted by lice or by ticks, the louse-borne and the tick-borne relapsing fevers consistently manifest epidemiological and clinical features which distinguish them The organism conveyed by lice is known as *Spirochaeta recurrentis*, and in nature it affects no mammals other than man It is conveyed from one man to another by the human body louse, *Pediculus humanus*, it gives rise to epidemic louse-borne relapsing fever, a disease preponderately of the cold and of the temperate climates The organism conveyed by ticks is known as *Sp duttoni*, of which possibly there are some varieties In some areas *Sp. duttoni* normally affects rodents and occurs only accidentally and incidentally as an infection in man In central Africa, however, it primarily affects man, in whom it is endemic In nature the tick-borne infection is not known to spread from man to man by means of the louse Nevertheless, within recent years the human louse, *P humanus*, has been infected experimentally with strains of *Sp duttoni*, and lice recovered from patients suffering from natural *Sp duttoni* infections have been shown to harbour the organism It has been suggested and it seems possible that a *Sp duttoni* infection in man might become adapted to transmission by the human louse, and so become an epidemic disease This so far has never been proved to occur in nature The regions in which the louse-borne disease and the tick-borne diseases normally occur usually are entirely distinct geographically, epidemic louse-borne relapsing fever has never been known to appear spontaneously in tick-borne relapsing fever areas of distribution without its introduction from an outside source

LOUSE-BORNE RELAPSING FEVER

DEFINITION

Epidemic or louse-borne relapsing fever is a disease due to infection with *Spirochaeta recurrentis*. The organism is conveyed from man to man by the human body louse, *Pediculus humanus* The disease is characterized by periods of fever with toxaemia, bodily pains, enlargement of the spleen and of the liver, bronchitis and jaundice These

Streptobacillus moniliformis infections: Arsenic is of no value in the treatment of these. Penicillin is specific, but there have been some reports of the occurrence of penicillin resistant strains of the organism. A dosage of at least 2 million units should be given. Aureomycin is said to be equally specific in the eradication of a *Strep. moniliformis* infection; the dosage is 0·5 gm six hourly for 10 days.

are refractory to infection with this organism directly on its recovery from man It can be introduced into, and maintained in, the usual experimental animals only after it has first been passaged through monkeys

The blood of a patient suffering from relapsing fever contains spirochaetes only during the febrile periods Lice feeding on the blood at this time become infected with organisms Immediately after the blood meal the engorged spirochaetes apparently disappear from the gut of the louse, they are believed to assume some developmental form, such as granules After
as spirochaetes d
insect is now infe
Female lice do not transmit their infections transovarially to their offspring, so individual lice must be infected by a blood meal before they can transmit the infection later to a fresh host

Infection of man rarely, if ever, results from the bite of the louse Lice damaged and ruptured by scratching liberate some of their contained spirochaetes, it is the entry of these through abrasions, probably

[illegible]

sing fever affords complete immunity to reinfection for a time, but this wanes and a second infection may occur even within a year of the first The disease in the endemic regions tends to recur epidemically at two or three year intervals, probably on this account

PATHOLOGY

In those dying of the disease jaundice is usual, and there are petechiae in the skin and the mucosal surfaces of the mouth There are petechial haemorrhages under the serous coverings of many organs, there are ecchymoses, which often are confluent, on the thickened and oedematous meninges The liver is much enlarged and hyperaemic The spleen, which is soft and congested, shows multiple infarctions and is much enlarged, at times its consistence may almost be fluid It contains miliary aggregations of mononuclear cells on the periphery of which are large numbers of spirochaetes There is cloudy swelling of all the organs, and there is fatty degeneration of the heart, the liver and the kidneys The immediate cause of death not uncommonly is a secondary bacteraemia with pulmonary infection or heart failure

Though spirochaetes are present in the blood when death occurs during the febrile period, they rapidly disappear from it On microscopical examination for some hours after death they can be found lying

febrile periods recur usually on one or two occasions The mortality is considerable

GEOGRAPHICAL DISTRIBUTION

Though primarily a disease of the colder and of the temperate climates of the world, where lice particularly abound, outbreaks of epidemic louse-borne relapsing fever have on occasions occurred in parts of equatorial Africa, in India, and in South America, where it is a disease of the cold seasons Serious epidemics have for long been known under conditions favourable to them to be a scourge in the temperate climates, and these frequently have occurred coincidentally with, or have closely followed, outbreaks of epidemic louse-borne typhus The epidemicities of these two devastating diseases have much in common; the starvation, overcrowding and squalor associated with famines, wars and other great human catastrophes favour major outbreaks of either or of both The geographical range of epidemic relapsing fever is rather wider than that of epidemic typhus, though the former has not gained entry into Australasia

AETIOLOGY

Many strains of *Sp. recurrentis* have been isolated from patients in various parts of the world during outbreaks of epidemic louse-borne relapsing fever On the grounds that these showed serological differences a variety of specific names have been attached to them. It is now known that differing serological responses, as revealed by agglutination tests, are engendered by the various phases of any single case of any [illegible] response to the [illegible] lapse; [illegible] these *The erection of new species solely on serological grounds is therefore* unwarranted There is every reason to regard the differently named organisms recovered from cases of epidemic louse-borne relapsing [illegible]

[illegible]

diameter 0 2 to 0 3 μ They are made up of spiral turns each occupying [illegible] of about 6-8

[illegible]

bent *Sp recurrentis* can be cultured on suitable fluid media *in vitro* and in the growing chick embryo The ordinary laboratory animals

disease is readily diagnosed, when suspected, by recovery of the spirochaetes from the blood during the periods of fever; they are absent from the blood during the afebrile intermissions of the disease. The parasites can be found in wet preparations by the Indian ink and similar methods, or by examination with a dark ground condenser. They can readily be seen in thick or in thin blood films stained with Leishman or with Giemsa's stain. They may be recovered by culture or by the inoculation of monkeys where facilities are available

TREATMENT

Prompt steps comparable to those employed in epidemic typhus must be to free the patient and all contacts from louse infestation

to treat patients with spirochaeticidal drugs when the crisis is due, as the tendency to collapse is greatly enhanced The attack is usually cut short by a single dose of arsenic, but if a relapse occurs a further injection should be given on its appearance It is unwise to give unnecessary doses of neoarsphenamine to a debilitated patient with evidence of liver involvement

Neoarsphenamine in this disease usually is given to an adult as a single dose of 0 4 gm to 0 6 gm intravenously The injection must be given very slowly In the event of a relapse of the disease the dose is repeated, possibly on one or two occasions at intervals of 4 or 5 days

Intensive penicillin treatment (20,000 units intramuscularly repeated at 3-hour intervals over several days) will terminate an attack of louse-borne relapsing fever, but it does not invariably prevent the subsequent appearance of relapses Penicillin cannot therefore be considered to be as therapeutically effective as arsenic

TICK-BORNE RELAPSING FEVER

DEFINITION

Non-epidemic relapsing fever is due to infection with *Spirochaeta duttoni* The organism may chiefly affect animals, from one to another of which it is conveyed by sundry ticks, under such conditions it occurs only incidentally and sporadically in man In central Africa, however, man is the principal and probably the only mammalian host, the infection is there conveyed from one man to another by ticks, and occurs as an endemic disease The clinical features of tick-borne

in the intercellular spaces and within endothelial cells throughout the body, particularly in the spleen, the Kupffer cells of the liver, and the endothelial cells of the lymph glands and bone marrow. If the examination is deferred for many hours none may be found

CLINICAL PICTURE

The incubation period ranges from 2 to 12 days; usually it is from 6 to 10 days After a prodromal period lasting a day or two the onset is sudden There is shivering, with severe headache, bodily pains, nausea and vomiting, and profound prostration. The temperature rises to from 102° to 104° F; usually it is of the continuous type, though it may be remittent. There is great thirst; the face is flushed; the eyes are injected; and commonly there is epistaxis. In severe attacks the spleen and the liver both enlarge, and they are tender. Jaundice is frequent. There is an increased respiration rate, with a cough and evidence of bronchitis. Sometimes there is an eruption on the trunk and limbs; this may be merely erythematous or it may be macular, in some cases it is haemorrhagic

The symptoms and signs continue over 4 to 9 days The temperature then suddenly falls to normal or subnormal, often with collapse of the patient. The symptoms and signs rapidly abate, the liver and spleen shrink in size, and the patient's condition begins to improve. There follows an afebrile period which lasts for from 4 to 17 days, usually about a week. This is succeeded by a relapse. This first relapse is similar to the primary attack but usually is of slightly shorter duration and lesser severity. Rarely it may be more severe than the initial attack and jaundice may make its first appearance during it. There is then another afebrile period, and this may be followed by a second relapse before the disease finally ends. In the majority of cases of louse-borne relapsing fever there is one relapse; in less than half of them there are two relapses; and in only 1 or 2 per cent are there three relapses.

The death rate from louse-borne relapsing fever is influenced by the age and the condition of the patient. In those who are ill-nourished and who live under bad conditions the mortality commonly is over 30 per cent in the absence of efficient care and treatment.

DIAGNOSIS

Outbreaks of louse-borne relapsing fever should always be anticipated on the appearance of an epidemic of louse-borne typhus. The

transovarially, thus the infection may persist through several generations of ticks It follows that only rare contact with a source of infection is necessary for the maintenance of the infection in a colony of ticks, and that members of the colony may be infective over very lengthy periods of time after the last contact with a mammalian source of *Sp duttoni* infection

When *O moubata* takes a blood meal containing *Sp duttoni* the organisms rapidly apparently disappear from the gut of the tick, after a time they reappear in large numbers in its body cavity or haemocoele In the female ticks spirochaetes can be found in the ovaries, as well as in its other solid organs, in this respect infection of the tick differs from that of the louse, where the spirochaetes are found only in the fluid media In ticks the invasion extends to the Malpighian tubes, or nitrogenous waste excretory glands discharging into the gut, the salivary glands and the saliva, and the coxal fluid In feeding, a tick pierces the skin and it excretes saliva, it evacuates its bowel towards the end of a meal, and it discharges coxal fluid By all these channels spirochaetes may be discharged on to the skin, they can then enter the wound made in feeding, or through other abrasions of the skin The spirochaetes also can pass through unbroken mucosa

PATHOLOGY

The pathology of tick-borne relapsing fever closely resembles that of the louse-borne disease

CLINICAL PICTURE

The onset and course of tick-borne relapsing fever are much the same as those of the louse-borne disease, with the following differences The intervals between the febrile paroxysms are usually rather less, being 8 to 12 days The febrile periods are also slightly shorter, but the fever tends to be higher, spirochaetes are less numerous in the peripheral blood [illegible]

more frequent and severe, these commonly take the form of facial palsy, a spastic paraplegia, iritis and severe diarrhoea and dysentery The tendency to haemorrhage is greater in the tick-borne than in the louse-borne disease In spite of these differences the mortality of the tick-borne disease on the whole is less than that of the louse-borne, this may well be due to the epidemic incidence of the latter among very debilitated persons living under abnormally bad conditions

Recovery from an attack of tick-borne relapsing fever is followed by

broadly resemble those of louse-borne relapsing fever; but the attacks are more severe, individually they are of shorter duration, and the relapses are more numerous

GEOGRAPHICAL DISTRIBUTION

In the Mediterranean countries, especially those of north Africa, and eastward to Russian Central Asia and northern India, in tropical and subtropical America, and in many of the United States, *Sp. duttoni* occurs enzootically in small rodents, and in other animals. Sporadic cases of human tick-borne relapsing fever occur in all these areas

In central, East, and South Africa tick-borne relapsing fever occurs endemically, the mammalian reservoir of infection being man himself and not rodents or other animals

AETIOLOGY

In those areas where the organism is primarily one of the rodent and animal populations it occurs only incidentally in man and is sporadic in its incidence Occurrence of the disease in man depends on his being attacked by ticks infected from animals. Some of the animals serving as reservoirs of the infection inhabit holes and caves, and the ticks harbouring there only rarely feed on man Humans entering the caves, however, are readily attacked by them, and whole parties of men doing so may be the victims of an outbreak of tick-borne relapsing fever. Other animals serving as reservoirs live in bush or scrub country, and trappers, travellers, campers, and others passing through the area are liable to become infested by ticks which normally feed on the animal population from which they have derived their infection

In central Africa on the other hand communities of ticks infesting human habitations become infected from a human being. Throughout these regions the infection though widely distributed tends to be a patchy or parochial one Persons spending the night in a rest house or on an old village site acquire the disease from the infected ticks there A neighbouring village site may be free from the infection The African disease differs from other forms of tick-borne fever in that so far as is known no mammal other than man, and the ticks themselves, maintains the infection

Sp. duttoni is morphologically identical with *Sp recurrentis*, but differs from it in some biological characters. It usually is readily inoculable into laboratory animals without preliminary passage through monkeys.

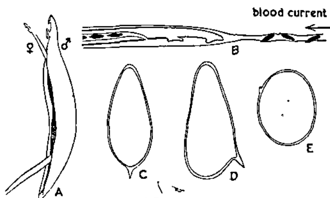
XXVI

THE SCHISTOSOMIASES

INTRODUCTION

A NUMBER of species of blood-flukes of the genus *Schistosoma* are parasitic in man in various parts of the world Three species, *S haematobium*, *S mansoni* and *S japonicum*, are relatively common parasites of man, some other species occur regionally or occasionally These rarer parasites include *S intercalatum*, *S bovis* and *S matthei* *S intercalatum* is found in man in the Belgian Congo, it produces terminal-spinal eggs closely resembling those of *S haematobium*, but it causes intestinal and not urinary symptoms *S bovis* and *S matthei* normally are parasitic in animals but they occur in man in certain localities

All these parasites outside the mammalian host undergo a multiplicative developmental cycle in snails Man acquires an infection by wetting the skin with water containing the infective cercariae shed by the snail hosts The cercariae actively penetrate the skin, find their way to the liver, and in the portal system and its ramifications develop into adult worms of two sexes The adult worms mature and live their sexual life inside the blood vessels The gravid female worms normally make their way to the terminal radicles of peripheral tributaries of the portal



[illegible]

substantial immunity to reinfection, but the immunity wanes and subsequent reinfection may then occur. Constant exposure of the indigenous population to infection and reinfection results in tolerance of the effects of the spirochaetes.

DIAGNOSIS

As for the louse-borne disease, but the organisms are less numerous in the blood though laboratory animals are more readily infected with them.

TREATMENT

The arsenicals are less effective in tick-borne than in louse-borne relapsing fever. The dosage with neoarsphenamine, given intravenously, should therefore be larger. A dose of 0.6 to 0.8 gm should be given as a single dose, and this should be repeated after a week, and possibly again after another week if deemed necessary. Intensive penicillin treatment may terminate the febrile attack, but it does not prevent the development of subsequent relapses of the disease

Aureomycin given orally, in doses of 0.5 gm at 6-hour intervals for 6 doses, produces prompt and dramatic symptomatic relief, and parasites vanish from the blood after the second or third dose. The drug should be continued for at least 12 hours after the fever has subsided; usually this is achieved after about 3 gm have been given Some relapses follow this treatment. It has been suggested that if the aureomycin dosage were continued over the more usual period of 10 days, the relapse rate would be further reduced.

Terramycin is extremely effective in curing mice experimentally infected with *Sp duttoni*. There is every reason to believe it will prove at least as effective as is aureomycin in the treatment of human cases of this infection

In hyper-endemic regions, with consequent heavy infestations, they cause much grave disability and the complications directly attributable to them contribute to the mortality In less intensely endemic areas it is stated that a very high proportion of the native population may be infested without complaining of symptoms or signs of an infestation with *S haematobium* or *S mansoni* Nevertheless, in view of the longevity (up to 20 years) of the worms, of their considerable egg production in that time, and of the histological changes due to accumulating unexpelled dead ova in the tissues, the consequences can hardly be dismissed as negligible

NON-HUMAN SCHISTOSOME DERMATITIS

There are a number of schistosomes which are parasitic in birds or in mammals, the life histories of these parasites in general closely resemble those of the human parasites Infection with them takes place by penetration of the skin by the appropriate cercariae, which have developed in snails In many parts of the world it is locally well known that bathing in certain waters gives rise to a severe skin irritation, and often eruption, known as bather's itch This condition in man is due to attack by the cercariae of non-human schistosomes which are parasites of birds and other animals These cercariae, although they will penetrate the skin of man and cause local lesions in it, do not develop further in him Some two dozen different cercariae have been identified as the cause of bather's itch in man, the adult worms and the snail hosts of most of these larvae have not so far been determined There is every reason to believe that many other so far unidentified cercariae also cause bather's itch

Penetration by the cercariae of the non-human schistosomes causes prickling or itching for an hour or so, with the appearance of small macules which may persist for some hours In some cases there is a diffuse erythema rather than a macular eruption, and occasionally there is a local urticaria Ten to fifteen hours after penetration papules may replace the macules, and the appearance of these is associated with intense itching for some days Sometimes after exposure to great numbers of cercariae the papules become confluent The papules usually disappear within a week, leaving pigmented spots On the second or third day vesicles may form, these are ruptured by scratching, and on bacterial infection they may become pustular In initial infections, both natural and experimental, schistosome cercariae may produce only a slight reaction, after repeated exposure to attack the reactions usually become much more pronounced, this is due to sensitization In highly sensitized individuals the reaction, even to small numbers of cercariae penetrating a very limited area of skin, may

venous system, dilating these small vessels as they ascend them against the direction of the blood flow. They then deposit their eggs one by one, retreating a little down the vessel after each egg is laid. The eggs normally are extruded from these vessels through the tissues into the bladder or the intestine, according to the location of the worms, and are voided to the exterior in the urine or faeces. They must enter fresh water or they perish; in fresh water a larva (miracidium) emerges from each of the viable eggs. The ciliated miracidia swim about until they find and penetrate a snail host appropriate to the species of schistosome. They actively penetrate into the snail and migrate to its liver gland. *Here the miracidia undergo further development and multiply, giving* rise in due course to large numbers of infective larvae (cercariae). Small clouds of cercariae are emitted by the infected snail; these swim, by means of a forked tail, in the water until they find the skin surface of man, they attach themselves, shed their tails, and penetrate. So, in due course, the cycle is repeated.

The species of schistosomes infesting man can be distinguished by *the morphology of the adult worms, to a considerable extent by their* sites of election in the body and the symptoms that result from the infestation, and by the morphology of the eggs they produce. The snails which serve as intermediate hosts differ with the species of the worm, they are limited in number and in geographical distribution, and are specific to each of the species of schistosomes.

The schistosomiases occur extensively among those whose activities involve entry into fresh water in the endemic areas. Primitive dwellings are always within easy reach of open water or rivers; there is pollution of these with infected urine or faeces, and pools, tanks, swamps and irrigation channels containing stagnant or slowly running water become extremely heavily infested with infected snails. The individual cercariae emerging from these in showers each survive about two days, but as they are constantly being renewed the water may become heavily charged with them. Children in view of their habits are particularly prone to expose themselves to infection. Though immersion of a part of the body in infected pools is a common means of infection, water drawn from them for domestic purposes is infective until stored for at least a couple of days, on taking freshly drawn water into the mouth the cercariae may attach themselves to and penetrate the buccal mucosa, infection equally may occur on wetting the skin with it.

Persons of either sex and of any age are susceptible to infection. *Males occupationally are as a rule more exposed to infection* than are women, male children are particularly liable to become infected. Previous infection confers no material immunity to superinfection or reinfection.

The material consequences of a schistosomal infection in man vary

other vector species of *Bulinus* of importance in some areas Other snails have been incriminated; among them are *Physopsis africana* in parts of South Africa, and *Planorbis dufourii* in Portugal

PATHOLOGY

The majority of the adult schistosomes dwell in the vesical, prostatic and uterine plexuses, which they reach from the liver through the inferior haemorrhoidal plexus Some enter the branches of the mesenteric veins, aberrant worms from time to time may be found elsewhere in the body Most of the ova produced in small vessels in the walls of the hollow viscera, with this species classically the bladder, pass through the tissues into the cavities of these viscera. In their transit they cause remarkably little damage Some may be carried in the blood flow into the systemic circulation, these lodge in the lungs and if numerous may ultimately cause pulmonary arteriolitis and pulmonary hypertension, or cor pulmonale Many do not escape into the viscera from the tissues, but die there within three weeks and calcify It is these which largely are responsible for the graver pathology of schistosomiasis Around the eggs lodged in tissue there is a cellular infiltration of eosinophil leucocytes, small round cells, and mononuclear cells A granuloma forms, with epithelioid and giant cells; there is caseation and calcification or fibrous tissue replacement of the granuloma Calcified dead eggs can be found in large numbers in the tumours The resultant lesions, seen readily by endoscopy in the trigone of the bladder, are bilharzial tubercles, these may ulcerate, and they cause papilloma formation, chronic fibrosis, and extensive calcification of the bladder wall The area involved, when the infestation is a heavy one, tends to extend peripherally The ureters, urethra, prostate and seminal vesicles become involved There is secondary bacterial infection and abscess formation of the affected area Chronic cystitis, an ascending pyelitis, and multiple sinus and fistula formation in the pelvis and perinaeum follow in neglected cases of heavy infestation of long duration Malignant changes may take place as a late sequel

[illegible]

are [illegible]

st [illegible]

Eggs have been recovered at one time or another from many organs of the body, notably the lungs, skin, liver and brain Some of these deposits may be due to the presence of aberrant female worms, but many are due to carriage of eggs in the circulation Though the ova of *S haematobium* are very rarely found in the stools, post-mortem studies have shown that in most cases of infection with this parasite they are present in the submucosa and mucosa of the rectum

be considerable; if large areas of skin are penetrated by great numbers of cercariae there may be a very severe generalized reaction with prostration. Some individuals do not become sensitized even after repeated exposures to cercariae over long periods; the reason for this is obscure.

Personal protection against cercariae is afforded by wearing rubber boots, or even by wearing a moderately tightly woven cloth. A film of oil or grease on the body is ineffective; indeed it encourages the attachment of those cercariae which normally penetrate the oily skins of water-birds. A thick coating of solid Vaseline is an effective preventive. The treatment of schistosome dermatitis is palliative. The antihistamine drugs are said to give relief, but further information on this point is necessary.

VESICAL SCHISTOSOMIASIS

DEFINITION

Urinary schistosomiasis is due to infestation of the vesical plexus with the trematode parasite *Schistosoma haematobium*. The disease is characterized by haematuria towards the end of micturition.

GEOGRAPHICAL DISTRIBUTION

Originating in the Nile Valley, where it is highly endemic, vesical schistosomiasis has become established widely though irregularly around the Mediterranean littoral, throughout Africa and the adjacent islands, and in Asia Minor; in all these regions suitable snail vectors exist. The disease does not occur in the East, nor in the Americas nor Australia. In India a focus of what is believed to be *S. haematobium* infection of man exists in Bombay province, here the vector is stated to be the snail *Ferrisia tenuis*.

AETIOLOGY

The adult *S. haematobium* commonly infest the vesical plexus. The [illegible]

Bulinus; *B. truncatus* is that most important in Egypt, *B. forskalii* is an-

CLINICAL PICTURE

At the time of penetration of the cercariae, especially if the number is large, there is an itching and pricking sensation with erythema (bather's itch or cercarial dermatitis) This usually lasts for no more than two or three days and is less severe than that due to the penetration of non-human schistosome cercariae

Some four or more weeks later there is a stage of toxaemia, or anaphylaxis, with irregular fever, malaise and generalized pains, often with a generalized urticarial eruption A temporary eosinophilia of 15 to 30 per cent is usual at this time This stage lasts from two weeks to two months, and it varies in its severity

Usually three to six months, but sometimes a couple of years or more, after infection localizing symptoms due to the presence of eggs in the tissues, and the consequent lesions, make their appearance There commonly is some frequency of micturition, and intermittent terminal haematuria makes its appearance The haematuria is limited to the terminal few drops of urine, it is not associated with dysuria, but there may be urethral and bladder pain after the act of micturition Vigorous exercise before micturition makes the terminal haematuria more evident As papilloma formation and ulceration increase in the bladder it becomes irritable and contracted, there is frequency and precipitancy, in severe cases there is dribbling incontinence with the passage of increased amounts of blood and some clots, and pus, due to secondary infection, in the urine The bladder shows areas of calcification at its base, it may become so extensively calcified that in severe old-standing cases its whole outline can clearly be seen radiologically

With the increase in the lesions in the bladder signs of more generalized genito-urinary and pelvic involvement develop Damage to the walls of the ureters, and back pressure due to obstruction of their orifices, make them dilated and tortuous, an ascending bacterial infection causes pyelitis and pyelo-nephritis, the renal and ureteral involvement may end in uraemia Chronic inflammatory tumours due to secondary bacterial infection, with sinus and fistula formation, cause much damage to the affected structures in the pelvis Neoplastic changes are particularly liable to occur in the bladder The patient may eventually die after years of increasing suffering

The severity of vesical schistosomiasis varies very greatly Not all those suffering from it pass through the stages described, but these are commonly seen in those heavily infected and repeatedly reinfected in the hyper-endemic areas such as the Nile Valley In cases of light infestation the patient may suffer a minimum of inconvenience The individual worms live for twenty or more years, and the progress of the condition is often a very slow one over this period, even after this

Old standing *Schistosoma haematobium* infection in a West African aged 18 years



Fig 42
Dilated renal pelves and ureters



Fig 43
Contracted bladder with calcifications in wall

CLINICAL PICTURE

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period there may be increasing disablement when irreversible structural changes have taken place.

DIAGNOSIS

The terminal-spined eggs usually can be found by microscopical examination of the terminal drops of urine, taken preferably after some brisk exercise. They are sought for by asking the patient to urinate, and to pass the last few drops of urine into a glass. It is this specimen which is searched. Alternatively, the sediment of a twenty-four hour specimen of urine may be examined for them. An early morning specimen, after rest, does not contain so many eggs

Biopsy through a proctoscope of a fragment of rectal mucosa, which is teased out and examined microscopically, will yield *S. haematobium* eggs in most cases of infection; they may be found there when none can be found at the time in the urine Only rarely will occasional eggs be found in the faeces

Cystoscopy will usually reveal lesions at the base of the bladder. The cystoscope when being passed grates over the 'sandy patches' of calcification and bilharzial tubercle formation Material obtained from these lesions through an operating cystoscope will yield living or dead and calcified eggs

A complement fixation test of the patient's serum, using as antigen an alcoholic extract of infected snails' livers, is usually positive within a month of first infection. It is a group reaction and is not species specific.

Intradermal skin tests, using an antigen prepared from adult worms or from cercariae, have been developed Their interpretation may be difficult, the test is at present not a very satisfactory one for ordinary clinical purposes. As with the complement fixation test the response is a group one.

Eosinophilia is usual during the early invasion and toxaemic stages, but it is very inconstant thereafter. In the later stages of even very heavy infestations there may be none

TREATMENT

The first drug to be effectively employed in the specific treatment of schistosomiasis was tartar emetic It remains the most effective discovered up to the present. The salt originally used was potassium antimonyl tartrate, the sodium salt was later found to be as efficient and rather less toxic; sodium antimonyl tartrate is now generally used, and not the potassium salt. There are two ways of giving a course of tartar emetic. the classical, consisting of dosage over two or three weeks; and the intensive, which compresses the dosage into two or three days

The most effective method is as follows a first injection of 0 5 grain of sodium antimonyl tartrate is given intravenously in 2-6 per cent solution in 5 per cent glucose, a second of 1 grain is similarly given 48 hours later, subsequently, 2 grains are given daily until a total of about 30 grains has been administered The solutions must be prepared without autoclaving; each injection must be given intravenously with scrupulous care, as leakage of even a small amount into the tissues causes a severe and indolent inflammation with sloughing Each injection must be given slowly over a period of at least ten minutes, if given hastily it causes a spasmodic cough, a feeling of constriction in the chest, dyspnoea and a rapid pulse These side-effects are minimized if the drug is slowly injected If vomiting, diarrhoea, jaundice or syncopal attacks develop during the course of antimony treatment it must be stopped All patients must be kept recumbent during the injections and for some hours afterwards Antimony is contraindicated when there is marked heart failure, nephritis, cirrhosis or hepatitis, and fever or gross sepsis.

The intensive method is as follows the gross dosage for the course is 1 grain of sodium antimonyl tartrate for each 12 pounds of body weight, this is divided into 6 doses which are given intravenously at intervals over a period of 36 hours The immediate toxic side-effects are not greater in the well-nourished than are those resulting from the longer course This intensive treatment is quite effective in most *S haematobium* infections, and has certain obvious advantages Nevertheless, on balance, it appears to produce sterilization of the infection in a rather lower proportion of cases than does the prolonged course In the poorly nourished and heavily infected natives of the Nile Valley it is stated that the intensive treatment causes severe toxic reactions, this has not proved to be the case with more lightly infected and probably better nourished Europeans and Africans The intensive course is useful for children with veins accessible for injection, antimony is well tolerated by them

Antimony in the pentavalent form is of no value in the treatment of the schistosomiases, but certain other trivalent salts have proved [illegible]

[illegible]

for 6 days Stibophen (Fouadin), a 6 3 per cent isotonic solution of [illegible]

[illegible]

is an initial one of 1 5 ml; a second of 3 5 ml after 48 hours; and then 5 ml is given each alternate day to a total of 10 to 15 injections The

drug can be injected intramuscularly into the buttocks It is of particular value in children and others whose veins are inaccessible for the injection of tartar emetic.

Anthiomaline, or lithium antimony-thiomalate, is another useful trivalent antimonial This also is non-irritant and only slightly toxic, but is inferior to tartar emetic. It is given intramuscularly in doses of up to 2 millilitres (0 01 gm of metallic antimony) daily or on alternate days for 12 to 20 injections

Before the less irritant antimonials suitable for intramuscular injection were elaborated emetine hydrochloride had been much used as an alternative to intravenous tartar emetic. It is schistosomicidal but has to be given in excessive dosage (2 grains daily or on alternate days for an adult on 6 or 8 occasions) to achieve a result It is rarely used now

In endemic areas, where mass treatment of a population is necessary, the advantages of a drug which can be taken orally, over one that must repeatedly be injected, are obvious. The thioxanthones (Miracils) which contain no heavy metals or alkaloid, have been found to be effective when given by mouth; but those so far elaborated appear to be less regularly curative than are the antimonials They may cure *S haematobium* infestations but they rarely cure *S mansoni* infestations

The side-effects of Miracil treatment may be severe; they consist of giddiness and vertigo, epigastric pain and vomiting, colic and diarrhoea, anorexia and insomnia, tremors and muscular weakness, with

on any necessary
esses, fistulae or
e of the infection
involves periodical thorough re-examination over some years.

Personal prophylaxis against schistosomal infection lies in protection of the body surface and mucosae from exposure to cercaria-infected water All water drawn for domestic use should be boiled, or at least should be stored for three or four days, before use If entry into suspect water is unavoidable fully water-tight occlusive clothing must be worn, the cercariae will penetrate porous fabrics, but impregnation of these with certain repellents limits the risk of infection Communal prophylaxis consists of efficient sanitation to prevent snail infection, and
snails Drainage
umbers but it will
preciable periods
when imbedded in moist mud

INTESTINAL SCHISTOSOMIASIS

DEFINITION

Intestinal schistosomiasis is due to infestation of radicles of the inferior mesenteric vein with the trematode parasite *Schistosoma mansoni* The disease is characterized by dysenteric symptoms, and in severe cases by cirrhosis of the liver with enlargement of the spleen and ascites

GEOGRAPHICAL DISTRIBUTION

Like *S haematobium*, the related parasite *S mansoni* originated in the Nile Valley and has spread thence further afield Its present areas of distribution are rather more focalized than are those of *S haematobium* Though the two infections occur concurrently in many areas of *S mansoni* endemicity the latter parasite has not spread around the Mediterranean littoral and it does not occur in Asia Minor Nevertheless it is present over wide areas of Central and South America where *S haematobium* has not established itself

AETIOLOGY

The adult *S mansoni* commonly infest the branches of the inferior mesenteric veins in the walls of the large bowel The lateral-spined eggs escape from superficial vessels in the bowel wall into the lumen of the intestine, and are passed to the exterior in the faeces The eggs if deposited in water give rise to miracidia, these enter snails and undergo further development and vigorous multiplication to form cercariae, the latter emerge from the snails and actively penetrate the skin or mucosae of man, so causing infection

The snails in which *S mansoni* commonly develops are species of *Planorbis*, *P boissyi* is that most important in Egypt, but *P pfeifferi*, *P sudanicus* and some other species of *Planorbis* are also vectors Snails belonging to the closely associated genus *Australorbis* have proved effective vectors, *A glabratus* and probably other species of the genus are the intermediate hosts in South America and the neighbouring islands

PATHOLOGY

The adult worms reach the small tributaries of the inferior mesenteric vein from the portal [illegible]

[illegible] infestation With the more diffuse distribution

of the parasites the individual lesions are less pronounced, and they are less accessible to visual examination during life. Bilharzial tubercles, nodular submucosal thickening, ulcerations and papilloma formation may be seen in the lowermost part of the gut sigmoidoscopically Inflammatory tumours due to secondary bacterial infection may develop, the abdominal lymph glands often are enlarged, and they may contain some eggs.

The location of the worms, and the free drainage of the vessels in which they lie into the portal circulation, facilitate embolism of the eggs to the liver. As they lodge and die there the cellular reaction and subsequent fibrotic changes they provoke cause peri-portal cirrhosis In Egypt in cases of Mansonian schistosomiasis there is often a general hepatic cirrhosis; this possibly is partly due to the metabolites of the parasites, but it is largely contributed to by nutritional deficiency which is aggravated by the parasitic infection. The portal hypertension following fibrotic changes in the liver causes the spleen to enlarge; it may reach a considerable size (Egyptian splenomegaly) in cases of intestinal schistosomiasis

Eggs may lodge ectopically in many tissues and cause lesions in them. Ova have been found in the lungs and myocardium, in the spleen and pancreas, and in the kidneys and suprarenals. They may get into the brain or spinal cord and cause the formation of granulomatous space-occupying tumours Eggs found in the central nervous system may reach it embolically from paired adult worms in the lungs; or adult worms may actually be present in the vessels of the cord or brain; though no worms so far have actually been recovered from the latter site in man, they have been found in vessels in the brain in experimentally infected monkeys The central nervous system complications in *S mansoni* infection involve the cord rather than the brain of man

CLINICAL PICTURE

The stage of initial infection when the cercariae are penetrating differs little from this same stage in vesical schistosomiasis.

The stage of toxaemia, which follows a month or so later, is usually more severe than the corresponding stage of the urinary disease In [illegible]

[illegible]

Commonly there is a marked urticaria, several crops of weals appearing on any part of the skin and often on the oral mucosa. There may be a temporary angioneurotic oedema At this time also there may be swelling and tenderness of the liver. An eosinophilia of 30 per cent or more, with a total white cell count of at least 15,000, is usual This may

subsequently fall to normal, or some degree of eosinophilia may persist throughout the later stages of the disease

Two months to a couple of years after the initial infection, the time being dependent on the intensity of the infestation, the infiltrative stage becomes manifest Commonly the first evidence in severe cases is colic and diarrhoea, with the passage of blood and slime containing the characteristic lateral-spined eggs If there are numerous lesions low in the rectum this dysenteric diarrhoea is severe and is associated with marked tenesmus Exacerbations of the symptoms of intestinal schistosomiasis in the early stages tend to recur at intervals of two or three weeks There is anorexia and wasting The colon becomes thickened, spastic and tender, the liver at first is enlarged and tender, and the spleen is palpable In many cases there is irregular fever Symptoms of a pneumonic type are evident if the infestation is a heavy one and many ova are carried to the lungs

As the infection continues the engorged hypertrophied mucosa of the large bowel bleeds more readily, ulceration and secondary infection cause the appearance of pus in the motions, and polypoidal tumours develop in the rectum and tend to prolapse Inflammatory tumours can be felt within the abdomen, and the abdominal lymph glands become enlarged and palpable Sinuses and fistulae commonly form in the indurated perinaeum and buttocks in the latest stages of the disease

Hardening and shrinkage due to fibrosis may transform the affected gut into a fibrous irregular tube largely devoid of mucosa Increasing fibrosis in the liver causes it to shrink The portal hypertension due to cirrhosis causes the spleen to enlarge, and ascites develops There is increasing hepatic insufficiency and cholaemia, which may terminate the condition within a few years, or it may progress over 15 to 20 years and be brought to an end by intercurrent infection

The complications of intestinal schistosomiasis are numerous In addition to those occurring as a direct result of the presence of parturient female worms in the abdomen, eggs may be found ectopically in various organs and tissues The lesions sometimes found in the central nervous system, in contrast to those due to *S japonicum* infections, tend to involve the cord rather than the brain A transverse myelitis with various forms of palsy is the usual result in this case

The effects of *S mansoni* schistosomiasis, like those of the disease due to *S haematobium*, vary very greatly They are dependent on the numerical strength of the worms and on the sites of deposition and of lodgement of the eggs In the highly endemic areas of intestinal schistosomiasis the morbidity and mortality rates due to the disease are high, in the lightly endemic areas many persons harbour light infestations with no apparent inconvenience, in these latter cases the diagnosis may be made only incidentally

DIAGNOSIS

In cases of heavy infestation the lateral-spined eggs can usually readily be found in the blood and mucus in the motions Where the infestation is light repeated search over many days for flecks of blood or mucus on the exterior of the formed stools may be necessary to find the eggs. Various concentration methods have been elaborated for the examination of stools in such cases

One such is a sedimentation technique performed as follows 10 to 15 gms of stool are thoroughly emulsified in a small volume of water; this emulsion is suspended in at least twenty-five times its volume of 0 5 per cent glycerine in tap water. The suspension is poured through gauze to remove macroscopic matter. After three suspensions and decantations, occupying 2½ to 3 hours, the final sediment is sampled and examined microscopically.

Another method, which has the virtue of ease of performance, con-

[illegible]

to rise and to swim about in the layers of the water below the meniscus in the neck of the vessel They can be detected with a hand lens and suitable indirect illumination

Even with these and other concentration methods it may be necessary to examine daily specimens of stool over a month in asymptomatic cases of light infestation before the eggs are recovered.

Rectal biopsy, as performed for the diagnosis of *S haematobium* infection, is of great value in the definitive diagnosis of *S mansoni* infestation, and is probably the most effective method of recovering eggs in cases of this infection

The complement fixation and intradermal tests are the same as those employed in the vesical disease but neither is a satisfactory procedure for diagnosis

TREATMENT

The specific treatment of intestinal schistosomiasis is the same as that stated for the vesical disease, but *S. mansoni* infestations are more difficult to eradicate than are *S haematobium* infestations The intensive short course of antimony treatment, using sodium antimonyl tartrate, is rarely effective. The prolonged course of tartar emetic treatment therefore is preferable and should be used for the treatment of this disease, the gross dosage of the antimony salt employed should be increased from the 30 grains which usually are adequate in *S haematobium* cases to 35 or 40 grains if the patient will tolerate it The thioxanthones

(Miracils) have proved disappointing in the treatment of *S mansoni* schistosomiasis

The prophylaxis of *S mansoni* schistosomiasis is the same as that for the *S haematobium* disease

ASIATIC SCHISTOSOMIASIS

DEFINITION

Far Eastern or visceral schistosomiasis (Katayama disease) is due to infestation of radicles of the superior mesenteric vein with the trematode parasite *Schistosoma japonicum* The disease is characterized by visceral lesions with dysenteric symptoms, hepatic cirrhosis, enlargement of the spleen and ascites

GEOGRAPHICAL DISTRIBUTION

Limited to the Far East the disease is found extensively throughout the Yangtse basin and the south-eastern part of China It is prevalent in Formosa, the Philippine Islands, Japan and parts of Burma

AETIOLOGY

The adult *S japonicum* normally infest the branches of the superior mesenteric vein draining the mesentery and small intestine and the inferior mesenteric vein draining the large bowel

The eggs have no spine, but there is a small tubercle on one side of them Normally they find their way into the lumen of the bowel and are voided to the exterior in the stools They must get into water to develop further, and the cycle of their development is similar to that of [illegible]

in the Yangtse basin, and other species of *Oncomelania* are the vectors in the Philippine Islands

PATHOLOGY

The histopathology of *S japonicum* lesions is similar to that of the other schistosomal infections of man This worm is a more prolific producer of eggs than are those of the associated species, in view of this fact and of the distribution of the female worms in the body the

pathological lesions are more widespread and extensive. The organs involved are the small bowel and the mesentery, and essentially the upper part of the large intestine The eggs are very readily conveyed in the portal system to the liver, which invariably is involved in visceral schistosomiasis, the resultant cirrhosis causes portal hypertension with gross enlargement of the spleen The lodgement of eggs in the mesentery causes this to become thickened, and the lesions in this and other tissues in the abdomen in severe cases result in considerable derangement of the abdominal viscera Ectopic lesions due to *S japonicum* much more commonly occur in the central nervous system than is the case with *S mansoni* infections

CLINICAL PICTURE

The stage of initial infection by cercariae resembles that of the other human schistosomal infections

The stage of toxaemia may appear within so short a period as a week



FIG. 44

Hepatic cirrhosis, portal hypertension and ascites in a Chinese with *S japonicum* infection Note the prominent superficial abdominal veins

[Courtesy of *The Lancet*]

of this, and is severe There is a marked urticaria with angioneurotic oedema and fever, vomiting, a toxic diarrhoea, cramps in the right upper abdominal quadrant, liver tenderness, and a dry cough with dyspnoea The stage of toxaemia lasts for some weeks, and during it there is a marked eosinophilia

The infiltrative stage may follow on the stage of toxaemia without intermission The diarrhoea becomes more severe, and there is frequent passage of loose bloody mucoid stools which contain the spineless eggs There is often a continuing or remittent daily fever, anorexia causes wasting, and there is an increasing anaemia but a diminution or even disappearance of the earlier eosinophilia The colon often is palpable and tender, the liver and spleen are engorged, enlarged and tender As fibrous tissue replaces the earlier focal abscesses and bilharzial tubercles the acute symptoms diminish and the fever lessens or disappears As the liver becomes more cirrhotic it shrinks, portal tension rises, and the spleen increases in size The mesentery and omentum become thickened and fibrotic, and by binding down the colon may cause a constriction to appear across an otherwise swollen abdomen in the wasted subject There is thrombosis in the mesenteric and portal vessels, and this produces ascites, the superficial veins on the abdominal wall may be distended and tortuous Haematemesis and melaena often follow the rupture of varicose veins in the stomach and bowel Hepatic insufficiency and cholaemia may ensue, or a supervening infection causes death Ectopic localization of eggs is common in Asiatic schistosomiasis In the central nervous system the lesions tend to occur in the brain rather than in the cord, schistosomal granulomata cause the clinical manifestations of an expanding tumour, with Jacksonian attacks, optic neuritis, monoplegia, hemiplegia or quad-

related schistosomes of man

DIAGNOSIS

Eggs can be recovered from the stools usually with greater ease than in the case of *S mansoni* infections The same methods of search for them are employed Intestinal biopsy through a proctoscope, or preferably a sigmoidoscope, is one of the most quickly effective means of finding the eggs and establishing a definitive diagnosis of the condition

The complement fixation and intradermal tests are similar to those used in the vesical and the Mansonian diseases

TREATMENT

The specific treatment is the same as for *S. mansoni* infections, and it must be given thoroughly and early to prevent the development of the grosser lesions

Brain lesions may demand suitable surgical relief in addition to specific treatment to avert permanent functional damage. Similarly, portal shunt operations may be necessary to relieve an established portal hypertension after specific treatment of the worm infection has been given

Prophylaxis is as for the other schistosomal diseases.

XXVII

SICKLE CELL ANAEMIA INHERITED HAEMOGLOBIN ABNORMALITIES

INTRODUCTION

CERTAIN hereditary anaemias are associated with abnormalities of haemoglobin This group of anaemias includes Thalassaemia and certain diseases, of which sickle cell anaemia (or sicklaemia) is a notable example, in which the protein fraction of the haemoglobin molecule differs from that of normal haemoglobin

Electrophoretic separation of haemoglobins has identified many forms, each of which has been labelled by a capital alphabetical letter Thus normal adult haemoglobin is called Haemoglobin A, foetal haemoglobin, Haemoglobin F, sickle haemoglobin, Haemoglobin S and the letters, C, D, E, H, I, J, L, M and N also have been allotted

The synthesis of each abnormal haemoglobin is controlled by a [illegible]

[illegible]

gene may afford some protection against *P falciparum* malaria This may explain the very high incidence of the latter gene in some areas of Africa

In the normal subject the haemoglobin is mostly in the form of [illegible]

[illegible]

(sometimes in more than one form, for example SC) or a mixture of normal and abnormal, for example AS

The more important clinical conditions are described below

1. SICKLE CELL ANAEMIA OR HAEMOGLOBIN S DISEASE

Sickle cell anaemia occurs in the homozygous state SS, in which the haemoglobin is nearly all Haemoglobin S, the remainder being F. In the homozygous individual there is no Haemoglobin A

PATHOLOGY

Relatively slight reduction in oxygen tension causes Haemoglobin S to crystallize, so contorting the erythrocyte into the characteristic sickle shape This sickling leads to intravascular stasis and occlusion, increasing blood viscosity and varying degrees of local ischaemia and



FIG 45 Sickle-cell anaemia, showing filamentous processes, 12 hours at 37° C

anoxia, associated with infarction, thrombosis, degeneration, necrosis and haemorrhage. Intravascular haemolysis occurs, together with active erythrophagocytosis and impedance of local circulation resulting from the sickling, thrombosis and embolism These processes may proceed in any organ

[illegible] isically due to these patho-
termined by the functional
infarcts in local areas of
tissues, haemorrhage, necrosis, and sometimes ultimate fibrosis can

occur in any part of the body, including the spleen, liver, kidney, bone marrow, bone, gastrointestinal tract and the brain

Homozygotes seldom live beyond the early years of life In those that survive to later years, the intermittent impairment of tissue blood flow results in some organs in the gradual replacement of the parenchyma by fibrous tissue The spleen, for instance, is enlarged and congested in early life, with the pulp packed with sickled cells, and the sinuses compressed to 'tiny chinks in a sea of red blood cells' The malpighian corpuscles are compressed and inconspicuous, and there are scattered areas of peri-follicular haemorrhages, later, following infarct, necrosis and fibrosis, the organ becomes smaller and the architecture is lost and replaced by dense bundles of fibrous tissue enmeshed in which are areas of iron-containing brown pigment, sometimes enclosed within a giant-cell reaction The small 'siderofibrotic' spleen seen in these cases is unique to sickle cell anaemia It may ultimately be much smaller than normal

The liver is usually large and congested even in adults, with cellular infiltration of the portal tracts and scattered centrilobular and focal necrosis of the parenchymal cells The sinusoids are congested and dilated and may contain sickled erthrocytes enmeshed in a fine fibrin network Erythrophagocytosis by the Kupffer cells is prominent

Emboli may affect the pulmonary vessels and commonly involve the

medullary area between the tables is widened and a combination of cortical thinning, erosion and new bone formation leads to extensive bossing which gives a characteristic look to the head and the 'hair-on-end' X-ray shadow

exhibits active nor-
erythrocytes and

n other haemolytic
orthochromic anaemias Sickling occurs rapidly in blood on removal from the body The sickled cells adopt bizarre crescentic shapes with long filamentous processes, which are rarely seen in the trait There is marked decrease in osmotic fragility The sedimentation rate is raised but is usually less than would be anticipated from the anaemia

The plasma bilirubin is increased, but frank jaundice is not always present Other chemical changes in the blood are dependent on the

concentration falls to about 5 per cent

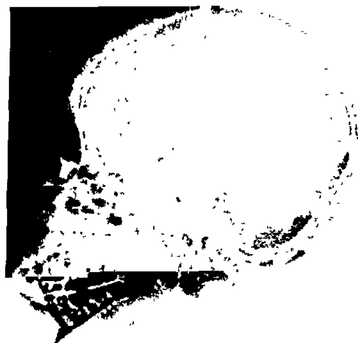


Fig 46
Skull changes in Thalassaemia Haemoglobin E Disease
The inner table is relatively unaffected The outer table is expanded Note the hair-on-end effect
[Courtesy of Dr Na-Nacorn, Siriraj Hospital, Bangkok]

CLINICAL PICTURE

Sickle cell anaemia usually becomes clinically evident about the third to sixth months of life, starting mildly but evolving rapidly Mortality is very high in the first three years. Relatively few patients survive into young childhood or adolescence.

In young infants the initial anaemia is not very severe Between six months and two years of age, however, it becomes progressively worse Crises during which the haemoglobin drops sharply to 2 to 5 gm per cent are common especially in the second six months of life and may be fatal These episodes are usually accompanied by fever, which is seldom high. Mild jaundice is common, with discoloration of the sclerae and deeply coloured urine.

The spleen becomes moderately enlarged and palpable and the liver less so Great enlargement of these organs is rare at this stage but there is usually further increase in size during the haemolytic crisis associated with local tenderness

Acute painful swellings of the bones of the hands and feet or of the limbs occur at intervals

Those who survive beyond the age of two usually live on for some years in indifferent health The child is more often ill than well, with a history of frequent bouts of fever or painful bones or joints Haemolytic crises occur at intervals and may be fatal A moderate degree of anaemia, e g 9-10 gm haemoglobin per cent persists in between the crises Occasional episodes of mild jaundice may occur, some children remain

[illegible]

persistent and may be incapacitating From time to time acute exacerbations with local swellings over bones or joints may occur

Death follows a haemolytic crisis or may result from intercurrent infection

Adolescent children and young adults may be found to have homozygous sickle anaemia They usually present a long history of poor health and repeated crises, but occasionally there may be no obvious history of previous attacks

At this stage the appearance is usually that of a thin underdeveloped asthenic individual with long thin limbs, delicate hands and feet and poorly developed secondary sexual characters Limb pains are often very severe Transient arthropathies occur in some patients, making the picture (apart from the anaemia) not unlike that of acute rheumatism

Haemolytic crises occur, but are less common and tend to be less severe than those in earlier age groups In between crises, the anaemia remains at a moderate level, the haemoglobin concentration falling considerably during the crises and returning to its previous level, but not to normal, after recovery from the haemolytic attack

Mild jaundice is common and may be constant The spleen may or may not be palpable; occasionally it may be considerably enlarged, especially in individuals who are suffering from frequent or severe haemolytic crises

Very few individuals survive to the third decade of life

[illegible]

million cells per cu mm. The thin film shows a great increase in nucleated erythrocytes, polychromasia associated with up to 20 per cent reticulocytosis, and, in certain cases, some macrocytes. Sickle cells are commonly seen in the film as elongate slightly curved 'cigar'-shaped cells 'Target' cells are usually present in variable numbers

There is frequently a mild leucocytosis of up to 20,000 cells or more per cu mm, with a shift to the left in the neutrophils.

The bone marrow shows a very active normoblastic erythropoiesis with no megaloblastic reaction. Sickled cells are common.

Haemolytic crises with precipitate fall in haemoglobin concentration occur in practically all cases The erythrocyte count drops to low figures, e g. 1 0 to 2.0 million cells per cu mm and there is nearly always evidence of intense bone marrow activity, resulting in the appearance of many reticulocytes and nucleated cells in the peripheral blood. Crises occur more frequently in infants in whom they may be the earliest clinical sign. They vary in severity but may be fatal at any age. Crises are accompanied by fever and some degree of jaundice, which may become severe with bilirubin in the urine and deviation of standard liver function tests The liver and spleen may enlarge during the crisis and become painful and tender Severe exacerbations of bone and joint pains are common

Bone changes are common and repeated in infants They become less frequent in older children and adults. Clinically there is local swelling, heat and oedema over the affected part, appearing rapidly, reaching a maximum in a week or so and usually subsiding without treatment in a few weeks, sometimes with residual thickening and tenderness, sometimes with complete resolution. In the active stage there is fever and very severe local pain Common sites affected are one or more of the metacarpals or metatarsals, or the fingers. The long bones, especially radius and ulna, the tibia and the fibula, are more often involved in older children The affected bones show increase in periosteal bone and rarefaction of the medulla, in older children permanent irregularities of periosteal bone are common. Necrosis may occur, for instance in the head of the femur or in the acetabulum Spontaneous fractures may occur and coarsening of the trabeculae, thinning of the cortex and lines of arrested bony growth are often seen It is thought that these changes arise from thrombosis of the local vessels and associated necrosis of areas of bone

Characteristic changes are seen in the skull bones 'Bossing' of the bones, especially the frontal temporal and occipital, is common by the age of 12 to 18 months. The outer table is thinned, there is gross widening of the bones, the medullary space being filled with fine vertical bony spicules, giving a 'hair-on-end' appearance. The inner table is unaffected. Comparable changes may occur in vertebrae The

changes are believed to be due to the increased vascularity of the overactive bone marrow

Changes in joints also occur, especially in adolescents, in whom there may be small effusions and associated periarticular inflammatory reactions

Cardiac dilatation may occur, usually after the age of infancy Chronic cardiac failure sometimes occurs in cases with persistent severe anaemia Acute circulatory collapse may develop during a haemolytic crisis

In some regions, for instance in West Africa, older cases sometimes complain of severe upper abdominal pain, with vomiting, low fever, and hepatic and splenic tenderness This syndrome probably results from vascular abdominal crises It is said to occur in double heterozygous sickle states, for example SC disease, more often than in homozygous SS states

'Sickling crises' which have also been reported in adults in West Africa, in which the spleen enlarges suddenly with violent local pain and tenderness, may also occur in mixed S haemoglobinopathies

Coma, convulsions and various sudden neurological pictures including hemiplegia have been reported in sickle anaemia Involvement of the nervous system is, however, relatively uncommon

2 SICKLE CELL TRAIT

The sickle cell trait occurs in the heterozygote, in whom half or less of the circulating haemoglobin is Haemoglobin S, the rest being normal Haemoglobin A

In most individuals, sickling does not commonly take place in the blood *in vivo* but it may be demonstrated *in vitro* Under suitable hypoxic conditions, for instance during flight at high altitudes, some intravascular sickling with its concomitant pathological effects may occur if a relatively high proportion of the haemoglobin is Haemoglobin S Under such circumstances it may initially be difficult clinically to distinguish between a heterozygote and a homozygote with sickle cell disease, but as a rule the former lives a normal life unaffected by his abnormal haemoglobin, unless some other heterozygous gene is also present (see below)

3 HETEROZYGOUS HAEMOGLOBIN S 'DISEASES'

The homozygous disease (sickle cell anaemia) has been described above The heterozygous trait may also become clinically important in



FIG 47 Sickle-cell trait 30 hours at 37° C.
(Courtesy of *Transactions of the Royal Society of Tropical Medicine and Hygiene*, London, and Dr H Foy)

individuals who are heterozygous to other abnormal haemoglobin genes. The combinations of Haemoglobin S : Thalassaemia and Haemoglobin S Haemoglobin C are the most important of these conditions. For instance the pathological processes and the clinical picture of SC. disease are similar in some respects to those in SS. anaemia; except that they are milder and in the former, iron deposition in the tissues is minimal, suggesting a less potent haemolysis.

4. OTHER ABNORMAL HAEMOGLOBINS

Homozygotes exhibit the 'disease', i e. CC , EE., etc. Most of these are clinically insignificant and may be discovered by accident Haemoglobin C disease, for instance, is characterized by a mild haemolytic anaemia, an increased number of target cells visible in stained blood films, some decreased erythrocytic osmotic fragility and pronounced enlargement of the spleen There are no serious occlusive or embolic phenomena, such as are characteristic of SS disease (sickle cell anaemia).

Heterozygotes exhibit the 'traits' and are important only in combination with certain other heterozygous genes, notably those of Haemoglobin S or Thalassaemia.

5. THALASSAEMIA

In this condition there is genetically transmitted interference with the synthesis of normal Haemoglobin A, but no abnormality of haemoglobin as such.

The homozygous state is called *Thalassaemia major* or Cooley's anaemia The affected children are frail, underdeveloped and rarely live to adolescence The clinical picture resembles that of sickle cell anaemia, with similar changes in the skull, but without the embolic phenomena The anaemia is severe and the blood picture closely resembles that of iron deficiency there is, however, no response to iron therapy The erythrocytes are normal in size or slightly microcytic, there is anisocytosis, poikilocytosis and there are many target cells Osmotic fragility is reduced Haemoglobin F is present in high concentration

The thalassaemia *trait* or *Thalassaemia minor* represents the heterozygous state There may be no clinical signs, but some subjects develop a mild hypochromic anaemia associated with an increase in target cells Haemoglobin A predominates in the blood, but there is up to 10 per cent Haemoglobin F and an increased fraction of Haemoglobin A_2

[illegible]

whom the abnormalities may be genetically independent The most [illegible]

Thalassaemia major

DIAGNOSIS

Diagnosis of sickle cell anaemia is made by a study of the familial, racial and geographical history of the patient and the clinical examination, by discovering evidence of the haemolytic anaemia by the demonstration of sickling and by analysis of the prevailing haemoglobins

The presence of a haemolytic anaemia is determined by examination of thin blood films and marrow smears The thin film reveals the



Fig 47 Sickle-cell trait 30 hours at 37° C
(Courtesy of *Transactions of the Royal Society of Tropical Medicine and Hygiene*, London, and Dr H Foy)

individuals who are heterozygous to other abnormal haemoglobin genes The combinations of Haemoglobin S. Thalassaemia and Haemoglobin S Haemoglobin C are the most important of these conditions For instance the pathological processes and the clinical picture of SC disease are similar in some respects to those in SS anaemia, except that they are milder and in the former, iron deposition in the tissues is minimal, suggesting a less potent haemolysis

4 OTHER ABNORMAL HAEMOGLOBINS

Homozygotes exhibit the 'disease', i e CC, *EE*, etc Most of these are clinically insignificant and may be discovered by accident Haemoglobin C disease, for instance, is characterized by a mild haemolytic anaemia, an increased number of target cells visible in stained blood films, some decreased erythrocytic osmotic fragility and pronounced enlargement of the spleen There are no serious occlusive or embolic phenomena, such as are characteristic of SS disease (sickle cell anaemia)

In sickle cell anaemia, Haemoglobin S represents the bulk of pigment present, the residue being Haemoglobin F There is no normal Haemoglobin A

In sickle cell trait Haemoglobin S usually makes up less than 50 per cent of the total haemoglobin, Haemoglobin A accounting for the remainder

'Mixtures' of abnormal haemoglobins, such as the double heterozygous states of SC, etc, can be distinguished only by complicated electrophoretic techniques, the 'S' moiety can of course be demonstrated by ordinary methods of determining sickling

The diagnosis of Thalassaemia is difficult The presence of a severe [illegible]

[illegible]

decreased

Excess Haemoglobin F is always present The clinical picture in a Mediterranean individual is characteristic – the underdeveloped child, with mongoloid features, splenomegaly and bony changes including pronounced bossing of the skull bones As in sickle cell anaemia, the patient rarely survives beyond childhood

The heterozygous Thalassaemia 'trait' is even more difficult to diagnose, since it is usually symptomless, except for mild anaemia and moderate numbers of target cells The amount of Haemoglobin F is [illegible]

[illegible]

TREATMENT

There is no specific treatment for sickle cell anaemia or the double [illegible]

[illegible]

restricted use in Thalassaemia or in the mixed haemoglobinopathies.

Chemotherapeutic agents have so far shown little activity in practice despite their occasional action in inhibiting or restricting *in vitro* sickling *Biscoumacetate*, in dosages which are sufficient to reduce prothrombin time, has been tried unsuccessfully. Trials with *Diamox*, a carbonic anhydrase inhibitor, have been equally inconclusive

characteristic picture described above. The marrow shows active erythropoiesis.

Sickling is rapid in sickle anaemia. Most cells are involved The sickled cells are thin and crescentic with filamentous 'tails'; in the trait only a proportion of cells sickle, sickling is slow and the sickled cells are blunt and leaf-shaped

Methods of demonstrating sickling are as follows:

METHODS

1. *Reducing agent* Make up a 2 0 per cent solution of sodium metasulphite (dithionite) in freshly distilled water. Take up a small volume of the solution in a pasteur pipette and suck in about one-sixth of the volume of blood. Blow on to a clean slide, mix thoroughly and cover with a coverslip Examine for sickling under $\frac{1}{6}$ in objective. Sickling will show in 3 to 15 minutes If there is none after 30 minutes the test is probably negative.

2 *Bacteria*. One drop of blood is added to one drop of turbid broth or a culture suspension of *B coli* or *B subtilis* and mixed on a slide A coverslip is placed over the mixture and the preparation sealed with petroleum jelly The mixture is incubated at 37° C and observed frequently. Sickling usually begins within 5 minutes. If none has occurred in 30 minutes the test is negative.

The rapid methods give quick results in both asymptomatic trait and sickle cell anaemia In the slow technique described below blood from sickle cell anaemia usually shows sickling long before blood from a carrier of the trait

3 *Moist stasis technique*. A drop of blood (usually from a finger which has been congested for a few minutes) is picked up on the under surface of a clean coverslip which is placed on a clean slide. The coverslip is ringed with petroleum jelly and the preparation is examined microscopically after 48 to 72 hours Cells from cases of sickle cell anaemia often begin sickling at once in such a preparation Cells from carriers of sickle cell trait sickle change only slowly

4. *In vivo sickling* Blood is withdrawn into a syringe containing oil, and is injected into isotonic formol saline also under oil The erythrocytes are regarded as being fixed in the shape in which they were circulating

Examination of the haemoglobins is made by some form of electrophoresis which is a purely laboratory procedure. The quantity of Haemoglobin F present can be estimated by various methods of alkali denaturation.

The lesions begin most commonly between toes, especially between the fourth and fifth They start as itchy erythematous areas over which vesicles appear and rupture. The affected skin rapidly becomes white and oedematous, the uppermost layers separate and peeling and cracking occurs, revealing a reddened hyperaemic thinly epithelialized base, which may ulcerate, crack and bleed The dead sodden epithelium exfoliates and is replaced by new layers which in turn undergo the same process The acute lesions are tender, painful and smelly

The dorsum of the foot and the plantar skin may eventually be involved

Secondary infection is almost always present and pustules may form with oedema of the surrounding tissues Sometimes there may be rapidly developing cellulitis, lymphangitis with adenitis, and generalized septicaemia

In long-standing cases the lesions become papulosquamous and hyperkeratotic with considerable scaling on a thickened sometimes mildly erythematous background Vesicles and pustules are absent except for occasional exacerbations of the lesions between the toes These changes in the skin appear most commonly on the plantar surface across the arch proximal to the toes along the sides of the foot and on the heel Such lesions seldom cause discomfort and may be unnoticed Their development may, however, be associated with exacerbations of the original lesions between the toes

The activity of the latter varies considerably from time to time The epidermis between the toes is usually swollen, white, sodden and macerated From time to time the dead smelly epithelium peels away revealing the moist reddened base Painful fissuring, especially in the web of the toes, is common Sweating between the toes is usually excessive especially when the patient is wearing leather shoes

After the subsidence of the acute phase the infection tends to persist for many years unless adequately treated, exacerbations occurring from time to time, especially during the hot season

Diagnosis Examination of scrapings from active lesions macerated in 10 to 20 per cent KOH solution will reveal mycelia or spores

Treatment Tinea pedis responds well to treatment. Mild lesions will heal in a few days Weeks may be needed in more chronic cases A few cases may be very refractory and reinfection from previously infected shoes, socks, floors, etc , is common

Treatment of the immediate lesions must be combined with manœuvres designed to minimize the chances of reinfection

Local Treatment In acute lesions, preliminary local treatment designed to reduce secondary infection is the first step The toes should be kept apart by gauze or cotton wool and dusted with aseptic powder between treatments, which should be carried out once or twice a day

XXVIII

SKIN CONDITIONS, MISCELLANEOUS

DERMATOMYCOSES AND SCABIES

DERMATOMYCOSES

DEFINITION

RINGWORM infections. Fungus infections of the skin, nails and hair caused by a group of closely related fungi, belonging to the genera *Microsporum*, *Trichophyton* and *Epidermophyton*.

AETIOLOGY

Fungal skin infections have a world-wide distribution They are *particularly common and severe in hot moist climates The fungi concerned* infect keratinized tissues and only rarely involve the subcutaneous tissues; they never cause systemic lesions.

In the affected tissue they appear as branching mycelial filaments and arthrospores They grow well on Sabouraud's medium after a fortnight at room temperature. The fungi may be primarily animal infections transmitted accidentally to man or primarily human infections Certain parts of the body are particularly prone to infection from any of the three genera of fungi. Clinical classification of fungal skin lesions is thus best based on anatomical distribution

Men are more commonly affected than women

The infections are spread by contact with active lesions, with infected hair, skin debris and peelings, especially in clothing, towels and floor coverings

Generalized cutaneous eruptions, resulting from sensitivity reactions, may occur. These are known as 'dermatophytids' or simply 'ids'

CLINICAL PICTURE

[illegible]

worst in the hot moist seasons and improve in the cooler weather. They are more severe in individuals who are constantly on their feet, especially if sweating freely and wearing badly ventilated boots or shoes Infection is spread by contact of bare feet with communal bathroom floors, towels, etc.

The lesions begin most commonly between toes, especially between the fourth and fifth They start as itchy erythematous areas over which vesicles appear and rupture The affected skin rapidly becomes white and oedematous, the uppermost layers separate and peeling and cracking occurs, revealing a reddened hyperaemic thinly epithelialized base, which may ulcerate, crack and bleed The dead sodden epithelium exfoliates and is replaced by new layers which in turn undergo the same process The acute lesions are tender, painful and smelly

The dorsum of the foot and the plantar skin may eventually be involved

Secondary infection is almost always present and pustules may form with oedema of the surrounding tissues Sometimes there may be rapidly developing cellulitis, lymphangitis with adenitis, and generalized septicaemia

In long-standing cases the lesions become papulosquamous and hyperkeratotic with considerable scaling on a thickened sometimes *mildly erythematous background Vesicles and pustules are absent* except for occasional exacerbations of the lesions between the toes *These changes in the skin appear most commonly on the plantar sur*face across the arch proximal to the toes, along the sides of the foot and on the heel Such lesions seldom cause discomfort and may be unnoticed Their development may, however, be associated with exacerbations of the original lesions between the toes

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Diagnosis Examination of scrapings from active lesions macerated in 10 to 20 per cent KOH solution will reveal mycelia or spores

Treatment Tinea pedis responds well to treatment Mild lesions will heal in a few days Weeks may be needed in more chronic cases A few cases may be very refractory and reinfection from previously infected shoes, socks, floors, etc , is common

Treatment of the immediate lesions must be combined with manœuvres designed to minimize the chances of reinfection

Local Treatment In acute lesions, preliminary local treatment designed to reduce secondary infection is the first step The toes should be kept apart by gauze or cotton wool and dusted with aseptic powder between treatments, which should be carried out once or twice a day

The foot should be bathed in warm permanganate solution (1 in 4000) or other antiseptic solutions and thoroughly dried. As much as possible of the dead epithelium between the toes and elsewhere should be removed with a rough towel. The affected area may then be painted with Castellani's paint or alcoholic gentian violet solution. There are now many efficient proprietary fungicides on the market. On the whole, a watery or alcoholic vehicle is preferable to an oily one, since the latter, as it melts, may sometimes carry infected material to the adjacent epithelium Oral therapy with the antibiotic 'Griseofulvin' is under trial

Over-vigorous treatment should be avoided as it may be followed by [illegible]

me [illegible]
should be continued for some time after local lesions have apparently healed.

[illegible]

sandals instead of shoes The use of personal towels only and the avoidance of walking barefoot in likely infective places such as floors and baths are very important The feet, especially the interdigital spaces, should be dusted at frequent intervals with aseptic powder containing 10 to 15 per cent calcium propionate.

2 Tinea unguium Fungus infection of the nails usually occurs in individuals already infected with fungus elsewhere, particularly in the hands and feet The infection develops slowly and is chronic and often extremely resistant to treatment. The toe nails are more frequently affected than finger nails [illegible] 'stal edg [illegible] 'esy epi [illegible] and scored The skin at the edges of the nails is often involved and shows active inflammatory reactions from time to time

Diagnosis (See p 332) [illegible]

to paper thinness and the part immersed in permanganate solution (1 in 4000) for half an hour each day After thorough drying sulphur or

[1] Whitfield's ointment contains 3 per cent salicylic acid and 5 per cent benzoic acid in a bland ointment base. Castellani's paint contains 8 per cent resorcin and saturated alcoholic solution of basic fuchsin made up in an aqueous 4 per cent phenol solution

salicylic ointments should be rubbed in gently Oral 'Griseofluvin' may be active Surgical evulsion or X-ray therapy may be necessary

3 TINEA CRURIS Dhobie itch groin or body ringworm Tinea cruris is found in the groin, crutch, perineum or perineal regions Similar lesions may appear in other areas, including the axillae and the folds beneath the breasts It may be caused by several fungi It commonly appears first on the inner aspects of the thighs and spreads rapidly to the perineum or scrotum and anal cleft The lesions may eventually involve large areas of skin, which become reddened, rough and scaling The advancing serpiginous edge is sharply defined, often raised, and may be papular or pustular The older lesions are flat, scaly and often brownish and discoloured in white skins

The lesion is intensely itchy and irritating and involuntary scratching commonly leads to secondary infection It may be so painful and uncomfortable as to interfere with walking, the patient proceeding on a broad base with legs well apart

Diagnosis is usually obvious from inspection Scrapings reveal fungal mycelia and spores (See p 332)

Treatment The lesions should be cleaned with soap and water

In the acute stage permanganate baths should be given twice a day, followed after thorough drying by aqueous gentian violet solution (1 per cent) and calamine lotion In more chronic cases Castellani's paint, 4 per cent gentian violet in 10 per cent alcohol, or half strength Whitfield's ointment followed by 10 to 15 per cent calcium propionate dusting powder will usually promote healing in a few weeks Tincture of iodine is an old remedy which is effective but severe and should be used only under medical supervision If any treatment excites an acute exacerbation it should be stopped immediately



FIG 48 Tinea cruris

Treatment should be continued for at least a week after the disappearance of the lesions If they are refractory to one form of treatment, alternatives should be tried

Local treatment should always be combined with precautions against reinfection which should include frequent changes of light underwear which will stand boiling

4 Tinea corporis Tinea circinata: body ringworm. Small well-defined annular erythematous papulosquamous lesions, varying in size from a fifth of an inch to two inches, appear on any part of the body They may be single or multiple and may coalesce to cover areas of skin several inches across. The central area is reddish and scaling; the advancing edge is elevated, vesicular and sometimes pustular. Old standing lesions may show thickening of the skin and hyperkeratosis The intervening skin is normal.

The infection may be acquired from animals It is commoner in children than adults.

Treatment The lesions are cleaned with soap and water twice daily. After drying, ammoniated mercury ointment (5 per cent) or sulphur and salicylic ointment (each 3 per cent) is rubbed in thoroughly. Tincture of iodine is also effective. Many modern proprietary compounds are successful

5. Tinea imbricata Scaly ringworm. This condition is seen particularly in south China, Ceylon, South Africa, South and Central America and the South Pacific Islands The lesions may be widespread over the body and are composed essentially of superficial slightly elevated closely set concentric rings of dry scaling skin which coalesce to form serpiginous patterns Diffuse eruptions in chronic cases have the appearance of ichthyosis. Diagnosis is obvious on inspection.

Treatment Whitfield's ointment and Castellani's paint or 10 per cent chrysarobin ointment are indicated twice daily. Response to treatment is slow and poor

6 Pityriasis versicolor. *Tinea versicolor. A superficial fungal* infection commonly seen in poorer sections of the populations of many tropical areas The most superficial layers of the skin are involved. There is little inflammation but considerable furfuraceous scaling In white skins the skin pigment in the lesion is deepened; in dark skins it is lightened The lesions occur as macules which vary in size from about a millimetre to several inches across and frequently coalesce. They are most commonly seen on the neck, shoulders, outer aspects of the arms and rarely on the abdomen

Superficial lesions with a white powdery scaly surface occurring in the common areas of distribution are diagnostic. The mycelia and characteristic grape-like clusters of spores may be discovered on examination of scrapings from the lesions

Treatment. Cleansing with soap and water, followed by any mild fungicidal application, is usually rapidly successful

7. Infections of the hair and scalp. *Hair included in an area infected with fungus will often undergo changes, becoming lustreless and brittle. Areas of alopecia are common when fungus infection occurs in the scalp.*

Infections of the beard hairs may lead to an appearance very similar to pyogenic *sycosis barbae*. Diagnosis is made by discovery of the causative organism. Treatment consists in shaving daily and the

8. TINEA CAPITIS is a fungal infection of the scalp which occurs in childhood and disappears after puberty. It begins as an erythematous papule through which passes a hair. The papules spread peripherally and coalesce. The hair becomes very brittle, splits and can be easily

poorer classes living in overcrowded conditions. It may be spread originally from cats and dogs.

Treatment is usually rapidly effective. Scales and crusts should be removed daily in soap and water. Infected areas should be covered with compresses of permanganate solution (1 in 4000) for half an hour. The head is then thoroughly dried and ammoniated mercury or sulphur-salicylic (3 per cent each) ointment rubbed in. Resistant cases are common and may need X-ray therapy.

9. TINEA FAVOSA. A fungus infection usually limited to the scalp but occasionally involving the skin and nails. It is found in filthy conditions, particularly in the Middle East.

The lesions are characteristically yellowish, and have cup-shaped crusts which emit a peculiar 'mousy' odour. Beneath the crusts are depressed moist red areas. Hair in the infected area is soon lost. In untreated cases the condition may involve the whole scalp and lead to scarring and baldness.

Treatment. Removal of infected hairs by epilation and the application of fungicidal ointments. The results are slow but satisfactory except for scarring. Lesions due to *T. favosa* unlike those caused by *T. capitis* do not resolve with puberty.

10. DERMATOPHYTIDS. Generalized secondary sensitivity eruptions may occur in subjects infected locally with fungi. A primary lesion containing the fungus is usually present, often in the feet. Fungi are not commonly found in the secondary lesions.

These lesions are known as dermatophytids or 'ids'. They usually

The commonest manifestation is the appearance of groups of tiny

deep vesicles filled with clear or cloudy fluid and lying along the fingers or in the palm of the hand (so-called cheiropompholyx) or of larger superficial vesicles or scaling areas The lesions itch intensely and scratching may lead to secondary infection with pus formation. The vesicles usually subside without bursting and are often succeeded by areas of scaling.

Occasionally there may be a generalized and itchy follicular papulo-vesicular eruption scattered over the back, buttocks, thighs and palms

Treatment. The reaction subsides as a rule upon treatment of the primary focus Overtreatment of the latter may exaggerate the 'id'.

Local treatment of secondary infection may be necessary.

DIAGNOSIS OF SKIN FUNGI

Many dermatomycotic infections may be diagnosed as such by clinical inspection The presence of fungi may be confirmed by the method described below. Detailed mycological identification of the offending fungus is a highly technical procedure.

EXAMINATION OF EPITHELIAL SCRAPINGS AND DEBRIS

Scales and epithelial debris should be scraped with a knife from the advancing edge of the active lesion. They should be placed on a slide and mixed or macerated with a solution of 10 or 20 per cent potassium hydroxide A coverslip is placed over the preparation and the slide is gently warmed The unstained material should be examined microscopically for hyphae and spores with the 2/3 objective, with the light cut down by partial closure of the diaphragm.

For further mycological investigation the material should be scraped on to a clean slide covered with another slide and wrapped in paper or gauze for transport

DESERT SORE AND CUTANEOUS DIPHTHERIA

DESERT SORE

A wide variety of inflammatory skin ulcerations is included in this term, including ulcers arising from pyogenic agents and others in which the principle organism is *C diphtheriae*. These ulcerations are seen most commonly in hot arid countries, including parts of Africa and Australia They appear singly or in groups on exposed parts of the body, especially the wrists and legs.

They vary considerably in size The surrounding skin is itchy and erythematous The edges are undermined, the ulcerated surface is yellowish and may be covered by a thin crust There is often a profuse seropurulent discharge The lesions are very persistent

Pyogenic organisms are present in all ulcers, in some *Corynebacterium diphtheriae* is present Ulcers of the latter type may represent primary diphtheritic lesions which have become secondarily infected, or vice versa Fusiform bacilli and treponemata are absent

Treatment consists in cleaning the ulcerated area and the application of local dressings containing sulphonamides, acriflavine or penicillin Indolent cases may respond to occlusive treatment as for tropical ulcer

When *C diphtheriae* is present, preliminary intramuscular injection of antitoxin is indicated

CUTANEOUS DIPHTHERIA

Skin infection with virulent strains of *Corynebacterium diphtheriae* causing ulceration is common in certain dry hot parts of India, Africa and the Middle East, and is occasionally observed in hot moist regions The infection may be spread from skin to skin or from the pharynx or vice versa It is not known whether the diphtheria organism initiates the lesion or gains entrance through an abrasion or existing pyogenic ulceration

Diphtheritic ulcers usually appear on the exposed parts, especially the legs They appear rapidly and tend to become chronic and indolent The lesion commences as a vesicle and rapidly ulcerates The ulcers are small, seldom exceeding a few centimetres across, rounded, clearly demarcated and may be multiple

The surrounding skin is erythematous or slightly bluish, and raised The edges are inverted and slightly undermined The surface is deeply ulcerated and usually covered with grey exudate or a dark crust

C diphtheriae can be demonstrated in the ulcerated tissue Bacteriological assistance is required for identification and estimation of virulence Pyogenic cocci and other organisms are commonly also present

Treatment consists of a single dose of 20,000 units of antitoxin intramuscularly and the application of local penicillin compresses Healing is rapid Sulphonamides and bland ointments are ineffective

Paralytic sequelae similar to those arising from faucial diphtheria have been reported

SCABIES

DEFINITION

The itch Dermatitis caused by infestation with *Sarcoptes scabiei*.

DISTRIBUTION AND AETIOLOGY

A world-wide complaint, especially common in some parts of the tropics and subtropics.

Sarcoptes scabiei is very small. The gravid female burrows into the epidermis and dies at the end of the tunnel after depositing eggs Larvae hatch in a few days and begin further burrows, eventually maturing in about 4 weeks Mating takes place on the skin surface and the 'cycle' is repeated, the resulting lesion developing rapidly through the activities of successive generations.

Transmission occurs by direct skin contact or through contaminated clothing or infested bedding

CLINICAL PICTURE

Intense local pruritus and dermatitis usually appear within a few days of infection The tissue reaction may, however, be delayed for weeks It is probably due to the burrowing, as the mite does not apparently produce noxious fluids The first visible lesion is a reddish black line a centimetre or more in length over which the skin is slightly elevated At one end an orifice may be visible At the other a tiny vesicle conceals the female

Itching is intense, especially at night, and frequent scratching and excoriation are followed by secondary infection Unless treated the lesions persist almost indefinitely and gradually spread from area to area

The mite can penetrate the skin everywhere, but is found most frequently where the epithelium is thin and delicate, especially between the fingers and toes, the backs of the hands, the wrist, the genitals, groin, breasts and axillae The head and neck usually escape

DIAGNOSIS

Examination of scrapings from lesions with a lens or the low power of the microscope may reveal the mite or bits of it The parasite may be most easily found by selecting for examination the white bleb usually to be seen at the end of a linear lesion It can often be dissected out with the point of a needle.

Scrapings are best examined on a slide after soaking them in 10 per

cent potassium hydroxide and covering with a coverslip The mite is pale, roughly globular, about 300 μ in length, has eight very short legs and numerous bristles

TREATMENT

Pyogenic infections must be treated as they arise

The parts affected or, better, the whole body except the head and neck, should be scrubbed or soaked once or twice in the day with soap and water (preferably Tetmosol soap) and thoroughly dried Sulphur ointment, benzyl benzoate or tetmosol are then applied

Benzyl benzoate An aromatic oily liquid is usually made up as a lotion with equal parts alcohol and soft soap It is rubbed in well,

satisfactory by itself as a therapeutic agent or prophylactic

PROPHYLAXIS

Cleanliness and avoidance of contact with infested bodies and materials are the first essentials

MYIASIS AND LESIONS CAUSED BY VESICAN BEETLES

MYIASIS

The skin may be invaded from time to time by the larvae of certain flies which burrow to the subcutaneous tissues and cause inflammatory lesions in which they mature, escaping for pupation after a variable time

In the tropics such lesions may be produced by *Dermatobia hominis* in tropical America and *Cordylobia anthropophaga* (the Tumbu fly) in parts of Africa The latter infection is spread by any means which expose the human skin to the first instar larva Dirty clothes, or clothes which have been dried in the shade may provide the opportunity for the larva to reach and penetrate the skin

The penetration of the skin is usually unnoticed. In a day or two a papule forms and grows into a furuncular swelling in which the larva becomes active at intervals, causing severe local symptoms, and the escape of serous fluid from the 'head' of the boil at which the posterior

end of the larva is presenting. The local lesion is fully developed within a fortnight. It is intensely painful and there may be local adenitis and even a general febrile reaction.

TREATMENT

A film of liquid paraffin is placed over the opening in the skin after removing any scab that may be present. The posterior end of the larva begins to emerge. More oil is added drop by drop. The larva tries harder to reach the surface for breathing and in doing so lubricates the walls of the lesion After a while it can be slowly expressed by pressure (often painful) on either side of the lesion.

Healing of the wound is usually rapid, but may leave some scarring.

The larvae of *Auchmeromyia luteola* (the so-called Congo floor maggots) hatch from the floor of native huts and attach themselves to those sleeping on the floors During the night the elongated dirty-white translucent larvae attach themselves firmly to the skin by means of spines and suck blood, changing colour during the process to bright red When replete, they drop off the victim and continue their development

Blow fly maggots may infest cutaneous lesions, bodily orifices, etc. Intestinal myiasis is mainly accidental.

Creeping eruptions somewhat similar to those due to aberrant round worm larvae may arise from cutaneous infection with the larvae or certain flies, for instance, from infection with the larva of the horse bot fly (*Gasterophilus* spp), each lesion containing a single minute larva, which has hatched from eggs deposited on the hairs, usually of the limbs The much larger larva of the cattle warble fly *Hypoderma bovis* may give rise to similar lesions (See p 489)

VESICANT BEETLES

Beetles belonging to the families *Cantharidae* and *Staphylinidae* are known to cause lesions of the skin which may be both inconvenient and severe.

[illegible] Spanish fly, [illegible] vesi-cant They are bright orange except for the head, very short wing cases and last two abdominal segments which are black. They are

widely distributed and known for their irritant effects, particularly in the Amazon valley and many parts of Africa Provided they are unmolested on the skin there is no cutaneous reaction If irritated or rubbed into the skin deliberately or at pressure points, such as the belt or shoulder areas, small bullae, blisters and raw tender ulcers develop after a latent period of about 12 hours The reaction is often mistaken for fungoid infections Particularly unpleasant results occur when the vesicant material is introduced into the eye A severe conjunctivitis with oedema of the lids and weeping is set up These insects have been suspected of causing blindness in young children

As in the case of other noxious creatures, some local knowledge of the genera and species, and their habits, is required before diagnosis can be made

XXIX

SMALLPOX

DEFINITION

SMALLPOX is a virus infection of cosmopolitan distribution, commonly met in the tropics and subtropics and of great importance to the health of the community because of its tendency to epidemic spread It is essential, therefore, to have a working knowledge of its epidemiology, diagnosis and treatment.

AETIOLOGY

The causative virus is small and exists in two main epidemiological forms The most pathogenic gives rise to the severe disease *variola major*, the less virulent to *variola minor* A third strain, *vaccinia*, is relatively non-pathogenic and is modified by passage through the calf for use in vaccines Severe and mild forms of the disease persist in certain endemic areas

Infection occurs via the respiratory tract and is spread by secretions and discharge from the skin lesions The disease is transmitted freely by infected clothing, paper and dust

The sexes are equally affected Any age is susceptible but in an unprotected community *the disease appears commonly in children*

CLINICAL PICTURE

The clinical picture of *variola major* is compounded of the toxic effects of the virus and those of secondary invaders of the skin lesions The *incubation period varies from 6 to 20 days.*

The onset is usually abrupt, often with rigor Headache and backache are common and severe, prostration is out of proportion to the fever In this stage the diagnosis is difficult, and the disease may be mistaken for influenza After 2 to 3 days, however, the rash appears As the eruption develops the toxic effects of the virus abate and are replaced by those of the secondary infection of the skin lesions. There is thus commonly a biphasic temperature chart

There may first be a general or localized flushing of peripheral vessels, often confined to the face and 'bathing trunks' area. In severe cases this flush may be accompanied by petechial haemorrhage The true rash appears *first on the forehead and often the wrists It spreads up* the fore-arms and legs and appears on the back of the trunk Its distribution is centrifugal There are more lesions on the legs than the thighs, on the forearms than the upper arms, on the upper half rather

than the lower half of the face The rash may follow lines of pressure, e g the belt-line, or scratch marks The axilla is usually free The whole rash comes out in the course of 48 hours at the most

The first lesions are reddish macules which may be mistaken for measles These rapidly turn into papules, vesicles and ultimately pustules The papules are rounded, up to a quarter of an inch across, hard and deep in the skin Many remain discrete, some become confluent In very severe cases the lesions may become haemorrhagic and widely confluent. They are ringed by a narrow irregular zone of erythema The vesicles are domed, not easily broken and do not collapse completely when broken Pustules, sometimes centrally depressed (umbilicated), form and eventually desiccate, leaving a crust, which in turn drops off and leaves some pitting The development of the lesions proceeds in roughly the order of their appearance, so that those on the face reach the pustular stage shortly before those on the trunk On the whole the lesions are thus all very much in the same stage of development at the same time The procession from macule to pustule takes anything from 5 to 7 days In very severe cases the lesions may be confluent In such cases the secondary infection is very severe and usually fatal



Fig 49 Smallpox
Note centrifugal rash distribution and evidence of photophobia
[Courtesy of Dr W H P Lightbody]

[illegible]

[illegible]

pa [illegible] drop out, sometimes weeks after the onset

The mucous membranes may become involved, especially those of the mouth and sometimes the pharynx and larynx (sometimes with acute oedema) and even the trachea Mucosal vesicles usually break down into shallow ulcers Vesiculation may appear in the mouth before it develops on the skin

There is often a mild generalized adenitis

Conjunctivitis and photophobia are early and severe in most cases Pustules may form in the conjunctiva and cornea The lids may be oedematous Keratitis may develop and spread rapidly, leading to corneal ulceration and occasionally sloughing of whole cornea Sight may be permanently impaired by these complications

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Infection occurs via the respiratory tract and is spread by secretions and discharge from the skin lesions. The disease is transmitted freely by infected clothing, paper and dust.

The sexes are equally affected. Any age is susceptible but in an unprotected community the disease appears commonly in children

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The clinical picture of *variola major* is compounded of the toxic effects of the virus and those of secondary invaders of the skin lesions. The incubation period varies from 6 to 20 days.

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the fore-arms and legs and appears on the back of the trunk Its distribution is centrifugal There are more lesions on the legs than the thighs, on the forearms than the upper arms, on the upper half rather

TREATMENT

There is no specific treatment for the stage of viral infection General nursing, feeding, etc , is of tremendous importance

The secondary infection of the pustules can be much modified by the early use of sulphonamides or penicillin The latter is much the superior once pus has appeared

All cases must be isolated and kept under fly or mosquito netting All secretions, scabs, etc., should be regarded as highly infectious and dust should be controlled as much as possible

Patients must be regarded as infectious until all lesions are healed and scabs separated

Prevention of spread in an outbreak should be attempted by vaccination of all contacts and other non-vaccinated persons Contacts should be quarantined for 16 days Vaccination may protect or lead to modification of the disease if performed within 4 or 5 days of exposure

Control of smallpox in a community is largely a matter of mass vaccination

COURSE AND PROGNOSIS

The outcome and length of the illness depend largely on the intensity of the initial virus toxicity and that of subsequent secondary infection (commonly staphylococcal)

In unprotected subjects, especially in children under 5 years old, the prognosis is bad; the death rate may be as high as 50 per cent in localized epidemics The severity of the disease is much lower in vaccinated individuals Vaccination in infancy will protect until about puberty.

Severe early toxic symptoms usually herald a severe attack The more severe the skin lesions the worse the outlook.

Absence of remission between the primary and secondary fevers is a bad omen

DIAGNOSIS

The body must be examined in a good light and the type and distribution of the rash carefully determined. The early severe toxaemia is often suggestive in an endemic area, especially during a known outbreak This is absent in chickenpox, which is perhaps the commonest source of confusion In chickenpox the skin lesions tend to come out in successive crops so that several stages of development are present at any one time The lesions are irregular in size, smaller than those of smallpox, roughly oval in outline, and very superficial The vesicles are easily ruptured, and empty completely. Surrounding erythema is distinct Vesicles mature in 24 hours The whole cycle from macule to scab takes only a few days and is often complete in two. There are fewer lesions on the extremities than on the trunk, on which the lesions first appear; the axilla is invaded; there are few on the hands and feet

The history of successful vaccination or otherwise should always be ascertained. *Successful vaccination less than 3 years previously is a* strong point against the diagnosis of smallpox. The early stages of the rash may be mistaken for measles or typhus, the papulo-vesicular

Laboratory diagnosis requires skilled observation.

Vesicular fluid or crusts may be collected for bacteriological identi-

by staining the scrapings of mucosal lesions, papules, vesicles, but not pustules This method helps to differentiate smallpox and varicella in which elementary bodies are few.

No pit between nostril and eye

Viperinae
(Vipers, adders, etc)

Pit between nostrils and eye

Crotalinae
(Pit vipers, rattlesnakes, etc)

(c) Fangs most posterior teeth in upper jaw. Head scales large Nostrils lateral

Colubridae (Opisthoglypha)
(Boomslang, tree snakes, etc)

Poisonous sea-snakes belonging to the family *Hydrophiidae* abound in certain Eastern waters and are a real hazard to fisherfolk Common genera include *Lapemis*, *Enhydrina* and *Hydrops*. These snakes have long thin bodies, a small head and large scales, practically no neck and a wide flanged tail

SNAKE BITE

The incidence of snake bite varies widely from region to region In many districts in spite of the large population of poisonous snakes, bites and fatalities are relatively uncommon In others bites are frequent and the annual death rate is considerable

Most bites occur on the extremities and many result from carelessness, such as putting hands into holes and burrows, or stepping over logs without looking Few snakes are aggressive, most get out of the way when disturbed They are nearly all nocturnal in their hunting habits, and many accidents result from walking in the dark without a light

The fear of snakes is very real in many tropical countries and natives are inclined to regard any unidentified injury to the feet, especially at night, as snake bite The psychological effect is often profound, the patient is sometimes shaking, sweating and shocked with fear. It is, therefore, except in obvious caes, usually necessary to make a careful examination to determine whether snake bite is present or not

Fang marks may give a clue In the case of elapines, vipers and pit vipers an unobstructed bite leaves two well marked fang punctures set about half an inch to an inch apart The bite is, however, not often fully effective and the skin may be torn, lacerated or scratched because of indirect aim or clothing Bites by opisthoglyphs usually show a row of teeth marks in front of the fang punctures A row of teeth marks only indicates a non-poisonous bite The latter should nevertheless be regarded seriously as secondary and sometimes anaerobic infection may result particularly after the bite of large snakes such as pythons

The effect of the bite is dependent on many factors, including its

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SNAKE BITE, SCORPION STING AND SPIDER BITE

INTRODUCTION

In what follows the effects of snake bite, scorpion sting and spider bite are discussed.

Many other poisonous creatures lurk in the tropics, including lizards (the Gila monster), toads, various anthropoda, poisonous fish, shell-fish and jelly fish Information concerning the effects of the respective envenomations, some of which may prove fatal, should be sought from appropriate local texts

SNAKE BITE

The specific antitoxic treatment of snake bite depends upon the rough identification of the snake. It is therefore important whenever possible to identify the suspected reptile. For this purpose the head and a few inches of the body are required For complete identification the snake should be preserved whole.

EXAMINATION OF THE SNAKE

First examine the teeth. It may be necessary to incise the mucosa to identify the fangs. Poison fangs are long sharp teeth set in the upper jaw They are usually single but may be in pairs or threes

Examine the head with care, using forceps and not fingers Venom remains active for a considerable period after the snake's death, and accidents have occurred through careless handling

The following simple key will help to identify the main groups of terrestrial poisonous snakes

(*a*) Fangs fixed in the upper jaw below or in front of the eyes If other teeth are present in the upper jaw, they are few and posterior to the fangs Head covered with large scales Nostrils lateral.

Elapidae (Proteroglypha)
(Cobras, mambas, tigersnakes, etc.)

(*b*) Fangs erectile on upper jaw, lying at rest retracted against the palate and pointing posteriorly Fangs often in pairs and usually the only teeth in upper jaw. Head usually covered with small scales; occasionally with large. Nostrils usually vertical.

. . *Viperidae* (Solenoglypha)

obstruction of the circulation must be swiftly applied In general the aim should be complete but intermittent obstruction of the blood flow by tourniquet

As soon as possible after the bite a tourniquet should be applied at a suitable point, i e above the elbow in the case of the forearm or hand and above the knee in the case of the leg and foot When the bite is on a digit a tightly-tied ligature proximal to the bite may be sufficient Tourniquets over the soft tissue proximal to the bitten area are probably of little use, unless an attempt is made to wash out the local toxin by the double tourniquet method A proximal tourniquet above the knee or elbow is pulled tight to obstruct all circulation A second tourniquet, loose enough to obstruct only venous flow, is placed above it, and a vein in the limb is opened The lower ligature is loosened for a minute or two and then tightened Bleeding takes place from the incised vein and local incisions and may wash out some venom

In any case, they should be removed as soon as more effective measures become available

Local Treatment The bite wound should be washed to get rid of any venom which may have spilled from the fangs at the time of biting

Incisions or suction over the area of the bite probably do very little good Indeed, some of the worst effects of non-lethal bites have resulted from inexpert incisions involving local nerves and vessels

The local application of chemicals such as the time-honoured permanganate crystals is useless and may aggravate the injuries sustained during biting or enthusiastic incision

Nevertheless, especially in viperine poisoning immediate attention must be paid to the bite wound, in order to minimize the necrotizing effects of the venom on the local tissues

For this purpose the local injection of antivenin or watery suspensions of soap, or of solutions of magnesium sulphate have been recommended The results are, however, equivocal, even with the local use of antivenin, which should not be used in any case if oedema is already present

The best results are obtained by cooling the bitten area as quickly as possible After application of the ligature or tourniquet, the limb should be washed and immersed in cold water almost solid with ice chips.

sequently the area

up to 24 hours

onged periodically

position, the accuracy of the attack, the deflection or otherwise of the snake's aim by clothing, the amount of venom injected, the physical state of the patient at the time of biting and the patient's age. The dose of venom injected depends to some extent on whether the snake has already been hunting before the bite occurs; bites in the early morning, for instance, may contain less venom than in the early evening at the beginning of the night's hunting. A snake may occasionally bite without injecting venom Children, other things being equal, are more seriously affected than adults.

VENOMS

The principal pharmacological effects of snake venoms are neurotoxic and haemotoxic. Some snakes inject only the former or the latter, the majority a mixture. Proterooglyph snakes inject largely neurotoxin,

involved early and may be paralysed. Autonomic effects are common and locomotion is often affected.

Haematoxins may produce shock, capillary bleeding, haemolysis and anticoagulation or coagulation or both. Local tissue damage, including bleeding, is more severe than with neurotoxins.

The fatal issue in elapine poisoning occurs quickly, i.e. within 1 to 3 days It may be rapid or delayed for a week or longer in viper poisoning Few opisthoglyph venoms cause serious intoxication.

The venoms of sea-snakes are basically neurotoxic but contain anti-

experimental scale; in the meantime some beneficial effect results from the use of cobra antivenin

IMMEDIATE TREATMENT

Immobilization: Venom is absorbed rapidly from the area of the bite and is distributed to the rest of the body via the lymphatics and venous

movement.

Tourniquet: Transport of the venom from the bitten tissues is often very fast; a serious or lethal dose may be absorbed in a matter of minutes after a successful bite. To be effective, therefore, artificial

than as alternatives Cortisone is given in doses of 50 to 100 mgm in 24 hours

The use of antihistaminic drugs during the shock of snake bites is sometimes helpful but care should be taken to avoid their hypotensive effects

SNAKE VENOM IN THE EYES

The fangs of certain cobras, particularly *N nigricollis* in Africa, are so designed that venom can be ejected at right angles to the length The snake instead of striking, 'spits' The stream of venom squirts for some feet and may strike the victim's face and eyes Painful conjunctivitis with rapidly developing palpebral oedema results and there may be serious consequences if the skin or conjunctival surface is broken, allowing penetration of the venom into the tissues

Treatment consists of washing thoroughly with bland solutions such as boric acid, or with milk or water Instillation of diluted antivenin often brings immediate or early relief

SCORPION STINGS

Many genera and species of scorpions are found in the tropics and subtropics All should be regarded as poisonous, although the size of the arthropod and the degree of toxicity of the venom varies widely from region to region

Scorpions shelter by day in warm dry areas under stones, in crevices in rocks, in wood piles, inside shoes and cupboards, etc They are most active at night

Stings are largely the reward of the careless and unwary and should be few and far between with reasonable care The poison is injected by a sting in the terminal abdominal segments usually with the tail bent forward over the body

In many parts of the world the incidence of stings is high, the mortality rate low In some districts there may be considerable mortality amongst children. Scorpion stings should always be regarded seriously

The signs of stinging are similar in all parts of the world, but vary greatly in degree Local reactions are severe in most cases General effects come on rapidly or may be delayed for some hours after the sting The effects of the venom are essentially neurotoxic and are displayed at their worst in young children

The sting leaves a single puncture It occurs most commonly in the legs and feet The local reaction is immediate and usually extremely painful A red wheal appears at the site, the surrounding tissues become

This cooling treatment greatly reduces local pain and is very effective in modifying the often disastrous local effects of the venoms of snakes such as *Echis* spp. and rattlesnakes.

FURTHER TREATMENT

The patient should be treated in hospital as soon as possible. Except for the limb being subjected to ice, the body should be kept warm

Antivenin should be administered immediately. It should be given intravenously where possible, otherwise intramuscularly. Specific antivenin is desirable but if there is no information regarding the species of snake, polyvalent serum must be given.

Information should be available regarding local poisonous snakes and every effort must be made to decide the nature of the snake concerned in any particular episode, in order to determine the best antivenin for use.

Proper precautions with regard to possible sensitivity to serum must be taken Some of the direst consequences of snake bite arise in fact from the treatment with antivenin Immediate anaphylactic shock is a dangerous hazard and serum sickness may develop a week to ten days after injection of the antivenin The short delay required for the determination of sensitivity by intradermal injection of 0 1 ml of the antivenin is rarely significant from the point of view of the envenimation If sensitivity exists, the antivenin must be administered in the usual gradually increasing desensitizing doses Only in extreme cases of poisoning is the blind use of antivenin justifiable.

GENERAL TREATMENT

Treatment of general effects is very important Haemotoxic venoms such as those injected by vipers frequently lead to severe shock or haemorrhage, which must be treated by intravenous restoration of blood volume with plasma or blood In cases of viperine bite, bleeding from the incised wound may be severe and a careful check should be kept on the blood loss Transfusion is frequently necessary Neurotoxic venoms, such as those injected by cobras, lead to respiratory failure and artificial respiration may be essential

Local pain may be relieved by cold and rest or elevation, but is often difficult to deal with, since depressive drugs including barbiturates and morphine may not be advisable. In some cases, however, they may be essential.

In elapine poisoning ergototamine tartrate may be helpful Coramine and other cardiac stimulants may also be given.

Prednisolone, cortisone and other allied substances have been used in the hospital treatment of snake bite with variable success They should usually be regarded as adjuvants to antivenin therapy rather

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This cooling treatment greatly reduces local pain and is very effective in modifying the often disastrous local effects of the venoms of snakes such as *Echis* spp. and rattlesnakes

FURTHER TREATMENT

The patient should be treated in hospital as soon as possible Except for the limb being subjected to ice, the body should be kept warm

Antivenin should be administered immediately. It should be given intravenously where possible; otherwise intramuscularly. Specific antivenin is desirable but if there is no information regarding the species of snake, polyvalent serum must be given

Information should be available regarding local poisonous snakes and every effort must be made to decide the nature of the snake concerned in any particular episode, in order to determine the best antivenin for use.

Proper precautions with regard to possible sensitivity to serum must be taken Some of the direst consequences of snake bite arise in fact from the *treatment with antivenin Immediate anaphylactic shock is a dangerous* hazard and serum sickness may develop a week to ten days after injection of the antivenin The short delay required for the determination of sensitivity by intradermal injection of 0 1 ml of the antivenin is rarely significant from the point of view of the envenimation If sensitivity exists, the antivenin must be administered in the usual gradually increasing desensitizing doses Only in extreme cases of poisoning is the blind use of antivenin justifiable.

GENERAL TREATMENT

Treatment of general effects is very important Haemotoxic venoms such as those injected by vipers frequently lead to severe shock or haemorrhage, which must be treated by intravenous restoration of blood volume with plasma or blood In cases of viperine bite, bleeding from the incised wound may be severe and a careful check should be kept on the blood loss Transfusion is frequently necessary Neurotoxic venoms, such as those injected by cobras, lead to respiratory failure and artificial respiration may be essential

Local pain may be relieved by cold and rest or elevation, but is often difficult to deal with, since depressive drugs including barbiturates and morphine may not be advisable In some cases, however, they may be essential.

In elapine poisoning ergototamine tartrate may be helpful Coramine and other cardiac stimulants may also be given

Prednisolone, cortisone and other allied substances have been used in the hospital treatment of snake bite with variable success They should usually be regarded as adjuvants to antivenin therapy rather

an inch long, the abdomen large and shiny black, marked ventrally with a characteristic red hourglass pattern The male is much smaller

The web is coarse and irregular and contains a tube in which the spider lurks. It is frequently found in corners and holes in barns and outbuildings Biting often occurs in outdoor privies

The effects of the bite vary considerably In many cases bites probably occur without notable symptoms but they may be followed by severe local and general reactions, the development of which has been watched experimentally by observers who have subjected themselves to biting

There may be local stinging pain, erythema and oedema Severe pain spreads rapidly from the bitten area to local muscles and eventually to the chest, abdomen and limbs Muscular spasms, especially of flexor muscles, cause the patient to double up Tremors and convulsions are common and severe Sweating and excessive salivation are common Vascular collapse may appear within a few hours of the bite There is frequently severe epigastric pain accompanied by abdominal rigidity The temperature rises, the pulse rate is fast and there may be profuse sweating

Deaths occur as a rule only in very young children

Treatment Antivenin has been prepared and used successfully by the intramuscular route Intravenous or intramuscular administration of 10 to 20 ml of 10 per cent calcium gluconate is said to relieve the muscular spasm Hot baths may also relieve the spasms

Arachnid poisoning has also been reported from Chile Here the active agent is the spider *Loxosceles laeta* The bite is followed by a severe painful erythematous oedematous local reaction sometimes associated with widespread oedema of the limb. Within a week blisters [illegible]

and involving especially the backs of the hands and the fingers, often

[illegible] a few fatal accidents.

oedematous and there may be some oozing of blood. In the first few minutes the pulse may be slow and lachrymation, nasal secretion and repeated sneezing are common. Sweating may be profuse. The skin is pale. There may be salivation, nausea and vomiting. The pupils are sometimes widely dilated. The patient complains bitterly of the local pain, is often dizzy and trembling. Central nervous changes develop in a few minutes to hours, with intense headache and restlessness. Local pain and tenderness continue, in some species local subcutaneous haemorrhage and even generalized petechial haemorrhage may be pronounced Coma and respiratory depression may develop in severe and fatal cases within a few hours of the sting Vascular collapse is a common terminal event after stinging by certain species. After recovery, which is usually a matter of 12 hours or so, the area stung may remain numb for days

TREATMENT

Information regarding the local species of scorpions and the availability of antivenin is important in a given district If possible, the scorpion should be killed and kept for examination.

Rapid local relief is often obtained by the subdermal injection of [illegible]

[illegible]

ing the poison by the early administration of specific antivenin, either subcutaneously or intravenously.

Sera made from horses are liable to cause anaphylaxis in sensitive individuals and must be administered with caution Bovine sera are sometimes prepared to minimize this risk.

Some authors recommend the combination of antivenin and a sympathicolytic drug such as Rogitin in severe general intoxication

SPIDER BITES

Most spiders have poison fangs but few are powerful enough to inject the venom through the human skin The bites of certain genera are, however, known to cause serious toxic symptoms and even death Details of poisonous spiders should be sought in the localities concerned, and only the briefest mention is necessary here.

The best known poisonous spider is the Black Widow, *Latrodectus mactans*, which is found in many parts of the world, including the United States, and parts of South America. As in most arachnid poisonings man is bitten only by the female. The body is round and about half

develop some time, even years, after the patient has left the endemic region for a more temperate climate

The classical picture was regarded at one time as primarily a disease of Europeans and those of mixed blood. Varieties of the syndrome, however, occurred frequently in Indian troops during the recent war. It is possible that the disease may have been previously overlooked in coloured communities.

Classical sprue rarely occurs in children, it is a disease of middle life. Women especially when pregnant are said to be more susceptible than men, except when the latter are under circumstances such as those of military service.

PATHOLOGY AND PATHOGENESIS

There is no convincing evidence of the existence of any specific infective agent. Previous or contemporaneous amoebic or bacillary dysentery or other dysenteric disturbances do not predispose to the appearance of sprue.

Certain features of sprue may be explained to some extent on the assumption of primary dietary deficiencies of one kind or another. It has been suggested, for instance, that the megalocytic anaemia of sprue arises from deficiency in extrinsic haemopoietic factor. The anaemia, however, often develops in cases in which there is no evidence of the exclusion of this factor, and the picture of nutritional macrocytic anaemia and not of sprue is the usual sequel of such deficiency.

Recently emphasis has been laid on the possibility that the syndrome originates from primary deficiencies of certain vitamins especially those of the B_2 group. These deficiencies might arise directly from inadequate intake or indirectly from non-absorption or defective intestinal biosynthesis. On the whole there is little evidence that deficiencies *per se* are a constant feature of the genesis of sprue. Unquestioned vitamin deficiencies do, however, develop in the syndrome and it is often difficult in a particular case to decide whether these are primary or not. The balance of the evidence suggests that they are not. The clinical picture of vitamin B deficiency differs from that of sprue. It appears wherever the deficiency exists, and are as common in Africa, where sprue is very rare, as in India, where sprue is endemic. Furthermore, the patent vitamin deficiencies in sprue can be restored without appreciable effect on the prevailing basic deficiencies in intestinal absorption.

It has recently been suggested that the vitamin deficiencies of sprue arise from interference with intestinal biosynthesis of the vitamins, resulting from redistribution of intestinal bacteria, which have been shown in some cases to flourish in the small intestine.

There is no evidence of primary endocrine dysfunction in sprue. The

XXXI

TROPICAL SPRUE. THE 'SPRUE SYNDROME'

DEFINITION

TROPICAL SPRUE: A metabolic breakdown of the gastro-intestinal tract of unknown aetiology. The fully developed classical case is characterized clinically by steatorrhoea, glossitis and stomatitis, dyspepsia, abdominal distension, rapid loss of weight and megalocytic anaemia

It is common practice to include as the 'sprue syndrome' other clinical conditions, such as those which were prominent in Burma during the recent war, in which certain features of the classical picture may predominate, while others may be absent

DISTRIBUTION

The sprue picture is found in parts of the tropics, subtropics and the New World, the distribution is regional rather than climatic. It occurs most frequently in parts of India, Burma, central and southern China, Indo-China, Ceylon, Java and Puerto Rico It has been described also in the United States, Central America, the Guianas, the West Indies, Japan, Hong Kong, Malaya, the Philippines and the Fiji Islands Isolated cases have been reported in Mauritius, Malta, southern Italy, the Middle East and in parts of Africa. During the war in India and Burma the 'syndrome' appeared in 'epidemic' form.

AETIOLOGY

Tropical sprue may have a very localized distribution in a given area It may, for instance, occur in several occupants of the same house, or in several members of one family A variant of the syndrome, the so-called hill diarrhoea, is sometimes seen in high altitude stations in India

There may be a seasonal variation in incidence, this was a notable feature of the Burma epidemics in the war.

Continued subsistence on inadequate diet is a prominent factor in the clinical history of certain forms of sprue On the other hand, the classical syndrome tends to develop most commonly in an economic group accustomed to a well-balanced and more than adequate diet.

The individual subject usually gives a history of having lived for some time, usually for years, in a recognized endemic area. Occasionally he may have resided in the region for only a few weeks. Sprue may

diffusely or largely replaced by pale fat-free and practically acellular tissue. Involvement of the spinal cord such as seen in pernicious anaemia is rare.

LABORATORY FINDINGS

Fat absorption. The stool usually contains excess total fat. Individual specimens may, however, have normal fat content. The rate of absorption of fat can therefore be determined only by a fat balance test, such as the following: The patient is given a charcoal marker and over three days receives in his diet a known quantity of fat (usually about 100 gms per day). At the end of the period a further marker is given and all faeces passed between the two markers are collected and mixed for estimation of fat content. The result is expressed as a percentage of the fat ingested.

The normal subject absorbs about 95 per cent of ingested fat, the sprue case absorbs considerably less.

Faecal fat is present as free fatty acids and soaps (split) and triglycerides (unsplit). The ratio of split to unsplit fat is high, i.e. 3 : 1 to 6 : 1 (normal about 2 : 1).

A simple alternative to the fat absorption test is the study of the absorption of vitamin A or Folic Acid, using standard methods.

Blood fat. The resting total fatty acid content is about normal. The total blood fat curve after a meal is low. The chylomicrograph (indicating particulate absorption) is flat in cases of sprue with diarrhoea; it may be normal in non-diarrhoeic cases.

Blood sugar. The fasting glucose concentration is often low. The post-absorptive curve for glucose is flat, the curve for fructose is normal.

The disappearance of glucose from the blood stream after intravenous injection is normal or slightly delayed.

Blood Electrolytes

Plasma inorganic phosphate concentration in the fasting patient lies within normal limits.

Serum sodium chloride and potassium tend to remain within normal limits until the late stages which may be associated with dehydration and shock. Under these circumstances the serum sodium values are low, the chloride also low but less reduced in proportion. Potassium concentrations remain unchanged.

Plasma calcium concentration may be low, especially in cases with tetany. Normal calcium values may obtain in some tetanic cases, in which the magnesium concentration is low.

Blood protein. In very advanced cases or in patients who have been living on diets deficient in protein the blood protein levels may be very low. The albumin content is principally affected.

low serum calcium and tetany sometimes present, and the flat glucose tolerance curve are due to absorptive defects The sodium and chloride deficiencies seen in late cases result from fluid and electrolyte loss and are not related to adrenal insufficiency

The primary disturbance in sprue seems to be defective intestinal absorption, involving particularly fat and certain carbohydrates.

It appears to be mainly the particulate absorption of fat which is at fault The intestinal juices contain their normal complement of enzymes and the splitting of triglycerides proceeds normally Because of the incomplete absorption of triglycerides, however, the quantity of free acids produced in the intestine is increased Unsaturated long chain fatty acids are absorbed in unusual amounts, possibly accounting for the excessive secretion of intestinal mucus which is believed to be responsible for the so-called 'deficiency' pattern seen in the barium meal. The more saturated acids are less well absorbed and cause intestinal irritation and diarrhoea Insoluble soaps are formed with calcium, leading to abnormal loss of that mineral. Bacterial invasion of the disturbed small intestine takes place and may lead, as mentioned above, to secondary avitaminosis

There is at present no good explanation of the origin of the absorptive defect There seems to be in some cases a temporary or inherent jejuno-ileal insufficiency of unknown origin similar to that arising in post-operative gastrocolic fistula It may be that the primary cause of *the defect varies from case to case Dietary faults such as the ingestion* of rancid animal fats, deficiencies, disturbances in intestinal enzyme metabolism, and changes in the intestinal flora may be concerned in the individual case.

Although it appears that the basic defect in sprue is failure of intes-

cases the latter may disappear before there is any notable clinical improvement

MORBID ANATOMY

There is nothing specific to sprue

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times reveals a decrease in absorptive surface, with flattening and coalescence of villi, and increase in numbers of goblet cells There may be a subepithelial cellular infiltration with plasma cells, lymphocytes and eosinophils. Oedema is common. These changes do not occur in idiopathic steatorrhoea. The red bone marrow may be increased

CLINICAL PICTURE

The clinical history reveals present or past sojourn in an endemic region There may or may not be evidence of sustained subsistence on a deficient diet

The beginnings of the syndrome may be so indefinite as to be missed altogether Frequently, however, there is an initial short afebrile attack of watery diarrhoea, or a series of such attacks with intervals of remission At this stage a mistaken diagnosis of food poisoning or dysentery is common

The motions during the diarrhoea are at first urgent, watery, pale, frothy and offensive A few motions only are passed in the day, commonly in the morning Immediate relief is commonly obtained by rest in bed and a high protein diet With or without such treatment remissions are to be expected, alternating with further periods of diarrhoea or looseness lasting a few days or weeks

Gradually the looseness or diarrhoea becomes a constant feature and the character of the stool changes slowly to that of the classical sprue stool, greasy, bulky, gaseous, soft, pale and foul-smelling Remissions frequently occur even at this stage, in which the diarrhoea and the appearance of the stool improve Eventually the condition becomes one of habitual looseness or mild diarrhoea Several stools are passed in the day, chiefly in the morning The desire for stool is urgent and the motion is passed explosively with accompanying large volumes of gas Defaecation is painless, but is commonly preceded by abdominal colic

This development of the syndrome from early diarrhoea is the commonest form of its appearance, but in some subjects, the diarrhoea may not develop until other features of the syndrome have appeared Thus loss of weight, dyspepsia or sore tongue may be the first indication of the onset

Dyspepsia at some stage is a constant feature It usually comes on after the diarrhoea and varies in intensity from one case to another and from time to time in the same case The patient complains of flatulence and abdominal discomfort especially after food Abdominal distension becomes marked, especially in the lower half of the abdomen, due to distension of the small intestine The dyspepsia and distension develop in severity during the day, becoming commonly more acute until the

s the abdomen

and peristalsis

il (The 'sprue abdomen')

Examination of the gastric juice may reveal achlorhydria at any stage This is frequently inconstant, and responds well to histamine In some cases the juice acidity is normal or high In the dyspeptic case a barium meal shows delayed gastric emptying and irregular

Prothrombin In severe cases the prothrombin index is often low and can be restored by the parenteral administration of vitamin K.

Blood Cells

Erythrocytes. In the developed case anaemia is present. The cell count usually ranges between two and four million erythrocytes per cu mm It varies considerably from time to time in individual cases.

The blood picture is one of macrocytosis, which may be pronounced, and some degree of aniso- and poikilocytosis The Price-Jones curve resembles that of pernicious anaemia The mean cell volume is raised above normal and the cell haemoglobin content is high.

The anaemia is thus hyperchromic with a colour index greater than 1 o. Occasionally it may be hypochromic.

Leucocytes show no characteristic changes.

GASTRIC JUICE

Free hydrochloric acid may be absent Achlorhydria is seldom histamine fast Occasionally there may be hyperchlorhydria The enzymes are normal

DUODENAL JUICE

Enzymes, pigments, bile salts are normal Emulsification of fat is normal Intestinal bacteria may be present in large numbers.

FAECES

The macroscopic appearance and fat content are referred to elsewhere Microscopic examination may reveal fatty acid crystals, fat globules and undigested food particles. The pigment content is normal; the pigments are present in colourless form The nitrogen content of the faeces may be high during diarrhoea

STERNAL BONE MARROW

In the anaemic case the marrow smear reveals megaloblastic and normoblastic hyperplasia In advanced cases the marrow may be very hypoplastic

URINE

The diastase content is normal The nicotinic acid content is low in clinically deficient cases. When salt and water deficiency has become established the usual changes in urinary chloride occur. In severe cases there may be no chloride. Urobilin, urobilinogen and porphyrin may be present in severely anaemic cases

especially over the forehead and malar regions and on the back and buttocks The nails are ridged and brittle.

In some cases the skin changes may superficially resemble those of avitaminosis, especially when they become prominent over the shin bones and scrotum The symmetrical lesions of pellagra, however, never develop in sprue. [illegible]
appear especially in the [illegible]
infections also tend to sp [illegible]

The appearance of anaemia is erratic It may develop early, occasionally it may be the presenting sign Most often, however, it develops after the diarrhoea and dyspepsia It is commonly of medium severity, varying considerably from time to time There may be haemolytic [illegible]

indicates a defect in production rather than excessive blood loss It is now considered that such anaemias may be additional to the syndrome arising from extraneous factors and are not essential to the basic picture of sprue In some cases there may be some iron deficiency and occasionally the anaemia may be predominantly hypochromic The hypochromic microcytic picture of secondary anaemia has not, however, been reported in sprue

Anaemia is seldom severe enough in itself in sprue to cause the patient to present himself for that reason It is usually the gastrointestinal [illegible]

He is difficult and unreasonable over his food and treatment and becomes very introspective, especially over his abdominal condition

Tetany with carpopedal spasm may appear irregularly, especially during periods of exacerbation of the gastrointestinal symptoms It is normally associated with a low serum calcium concentration, sometimes a low magnesium

Central nervous changes are uncommon Subacute combined degeneration does not occur Spastic paraplegia and peripheral neuritis arising from vitamin deficiency have been reported Neuritic pains and hyperasthesia and tingling in the arms and legs with tenderness in the calf muscles are not uncommon Impotence is common in the male

The final stages of tropical sprue appear months or years after the onset The progress of the condition is seldom continuous, there are usually irregular periods of remission of variable length during which the signs and symptoms may almost completely subside, only to reappear often more severely in successive stages of exacerbation.

clumping of the barium in the small intestine, instead of the normal feathering *This is the so-called 'deficiency pattern', which appears to* be caused by the presence of excess mucus in the gut. In a few cases the large intestine may show some dilatation and loss of pattern due to mural atrophy Megacolon, such as seen in coeliac disease or non-tropical sprue is, however, very unusual.

The appetite is one of the many inconstant factors in sprue. In the early stages there may be no change, but as dyspepsia develops, periods of anorexia become common. The patient may show a distaste for certain foods which experience has taught him exacerbate his symptoms Painful deficiency lesions in the mouth and oesophagus may emphasize his anorexia. Later, the appetite may return and the patient may become ravenous and make his condition worse by overeating and bad choice of food The appetite often recovers very early in treatment before any real clinical improvement is established.

The establishment of diarrhoea or looseness and dyspepsia is usually followed quickly by changes in the tongue and mouth Occasionally these may precede the gastrointestinal signs

[illegible]

and lips. The palate is infrequently affected The severity of the lesions varies from day to day but in the untreated case tends to progress, with irregular remission until the filiform papillae are eventually lost and the tongue becomes smooth, shiny and fissured In severe cases there may be persistent and inconvenient salivation and dribbling Sometimes the lesions may involve the oesophagus and lead to dysphagia and severe retrosternal discomfort on swallowing.

Secondary deficiencies of the vitamin B_2 group give rise to other changes in the mouth, which are commonly seen in advanced cases but may be absent These include cheilosis and angular stomatitis In cheilosis the lips, especially the lower, are inflamed and swollen, the mucous membrane is cracked and peeling, covered with small dark curled flakes of epithelium. Angular stomatitis occurs as cracks and fissures at the angles of the mouth, which are irritating and easily secondarily infected. Eye changes due to ariboflavinosis, including mild conjunctivitis, photophobia and lachrymation may appear in some cases.

Throughout the progress of the syndrome weight is rapidly lost and the patient becomes increasingly emaciated The skin eventually becomes dry, flaky and wrinkled and the subcutaneous fat disappears. Irregular patches of light brown pigment may appear in the skin,

In non-tropical (idiopathic) steatorrhoea the endemic history is missing, the calcium metabolism is grossly affected and osteoporosis is common Megacolon is much commoner than in sprue The anaemia and megalocytosis are generally less pronounced Response to treatment is poor Bone changes are rare in sprue, except in certain individuals who respond to gluten-free diet The glucose absorption curve in idiopathic steatorrhoea is of the 'flat' type

The effects of obstruction of the lacteal flow may closely simulate

accompanied by hypochromic anaemia and normoblastic marrow responses

In chronic pancreatitis the faeces contain a high percentage of neutral fat and the split fat content is low – the reverse of the situation in sprue The enzyme content of the duodenal juice is reduced and glucose absorption is normal or diabetic in type

The anaemia may be confused with that of pernicious anaemia or tropical macrocytic anaemia Steatorrhoea is absent, however, in these conditions Moreover, in pernicious anaemia profound central nervous

diarrhoea are often present in pellagra, but there is no steatorrhoea, and the classical pellagrinous symmetrical dermatitis is absent in sprue Other vitamin deficiency syndromes are also unaccompanied by steatorrhoea

COURSE AND PROGNOSIS

Sprue progresses after the onset by a series of remissions and relapses Great emaciation with dehydration and vascular failure are common in the late stages Intercurrent infection is often fatal In rare cases intestinal ulceration and perforation may occur

Response to treatment is usually rapid With co-operation from the patient clinical cure is usual The order of disappearance of signs and symptoms varies from case to case Diarrhoea usually clears quickly The blood is often very slow to regenerate fully The defect in fat absorption is frequently the last sign to disappear

Relapse may occur at any stage, even after apparent full recovery Cure should not be predicted for at least three years after treatment. The subsequent histories of treated cases indicate a high recovery rate. Prognosis, however, deteriorates with age

Eventually some vascular dysfunction develops, the blood pressures fall, there may be some right-sided dilatation of the heart and medical shock

Signs of protein deficiency may develop and serious dehydration resulting from mixed water and salt loss may dominate the closing stages. The patient shows the clinical features of dehydration, with inelastic skin, hollow eyes, tight drawing of the skin over the malar bones The state of dehydration may be confused with that of emaciation but examination will reveal a reduction in plasma sodium and chloride and often the absence of chloride in the urine. It is most important to demonstrate the dehydration since it can often be readily corrected and yet be fatal if missed.

Vascular failure, with rising pulse rate, falling blood pressures and loss of circulating plasma volume and associated haemoconcentration is common in the advanced case. It may be accompanied by oliguria, or anuria and acute uraemia

The '*sprue syndrome*' During the second world war in the Burma campaign Indian and European troops were affected by a group of syndromes diagnosed as sprue In the field the cases did not present all the elements of the classical condition, but defective intestinal absorption, especially of fat, was a constant feature. The clinical picture was highly erratic, and often differed considerably from the classical syndrome This was probably due partly to the early stage at which cases were seen, and possibly to the prominence of certain special aetiological factors consequent on war-time conditions. The relative emphasis and order of appearances of signs and symptoms in the individual subjects varied widely Some cases which were evacuated to Europe subsequently developed the classical picture of sprue. The syndrome appeared as a rule after periods of some months' subsistence on inadequate or frankly deficient rations 'Epidemics' occurred in some areas, the peak of incidence falling in May, June and July The relation of the 'syndrome' to classical tropical sprue has not yet been clearly defined.

DIAGNOSIS

The clinical diagnosis in the individual subject is made on the history (sojourn in an endemic region at some period is essential) and the demonstration of intestinal absorption defects

Conditions likely to be confused with sprue are other steatorrhoeic states, macrocytic anaemias and vitamin-deficiency syndromes

In children coeliac disease resembles sprue in some ways The steatorrhoea is of the same type, but the anaemia is mild and usually hypochromic and response to liver treatment is poor.

(ii) MEAT DIET (Fairley)

Rump steak after removal of obvious fat is minced and lightly cooked in a pan in its own juices without the addition of cooking fat This mince constitutes the essential ingredient of the diet in the early stages Later the meat may be served unminced and fish and chicken may be substituted occasionally

Details

Diet No 1 (Calorie value = 770) 8 a m – underdone beef 3 oz, rusks ¾ oz, juice of ½ orange+glucose 2 drachms

12 noon – soup 4 oz+liver extract (= ⅜ lb), underdone beef 3 oz, rusks ¾ oz, juice of ½ orange+glucose 1 drachm

6 p m – The same as at 12 noon

Protein fat carbohydrate = 1 0, 0 3, 1 2

Note – When patients are very ill, two-hourly feeds of meat and beef-juice can be substituted

Diet No 2 (Calorie value = 1280) 8 a.m – underdone beef 5 oz, rusks 1 oz, calves-foot jelly 2 oz, juice of 1 orange +glucose 2 drachms

12 noon – soup 4 oz+liver extract (= ⅜ lb), underdone beef 5 oz, rusks 1 oz, juice of 1 orange+glucose 2 drachms

4 p m – tea 10 oz, milk 2 oz

7 p m – The same as at 12 noon+calves-foot jelly 2 oz

Protein fat carbohydrate = 1 0, 0 3, 1 0

Diet No 3 (Calorie value = 1820) 6 a m – tea 10 oz, milk 2 oz

8 a m – underdone beef 6 oz, rusks 1½ oz, calves-foot jelly 2 oz, juice of 1 orange+glucose 2 drachms

10 a m – 1 baked apple+custard 1 oz

12 noon – Soup 4 oz+liver extract (= ⅜ lb), underdone beef 6 oz, calves-foot jelly 2 oz, rusks 1½ oz, juice of 1 orange+glucose 2 drachms

4 p m – Tea 10 oz, milk 2 oz, 1 baked apple 1 oz+custard 1 oz

7 p m – The same as at 12 noon

Protein fat carbohydrate = 1 0 0 32 1 3

Diet No 4 (Calorie value = 2200)

6 a m – Tea 10 oz, milk 2 oz

8 a m – Underdone beef 7 oz, rusks 1½ oz, calves-foot jelly 2 oz, juice of 1 orange+glucose 2 drachms.

10 a m – 1 baked apple+custard 2 oz.

12 noon – soup 5 oz+liver extract (= ⅜ lb), underdone beef 7 oz, calves-foot jelly 2 oz, rusks 3 oz, juice of 1 orange+glucose 2 drachms.

4 p.m – tea 10 oz, milk 2 oz, 1 baked apple+custard 3 oz

In some cases the 'syndrome' may go on to the full picture of sprue. It responds well in the early stages to chemotherapy (see p. 365).

TREATMENT OF TROPICAL SPRUE

The patient should be treated in bed in the early stages, preferably in hospital He should be kept quiet and at rest and under discipline so that his treatment can be carefully supervised. He should be discharged as early as possible, *since he tends to get neurotic and gut* conscious; occupational therapy is advisable.

DIET

Diet is the basic element of treatment It should contain high protein, low fat and carbohydrate content roughly in proportion 1 . 0 3 . 1.

The source of protein may be either milk or meat. Patients will be found to vary in their response to milk and meat, but once the form of the diet in the individual case has been determined the patient should be persuaded to keep to it

The diet should be increased in stages, as outlined below, the rate of increase depending on the clinical progress. Favourable response is indicated by lessening of the gastrointestinal symptoms, improvement in the appearance of the stool and gain in weight.

Tropical sprue does not respond to a gluten-free diet Some weeks will probably have to be spent on each stage of the diet.

(1) MILK DIET (Manson-Bahr)

The natural fat in milk is usually well tolerated, this may not be so with separated cream or butter If fresh milk is not well accepted, defatted dried milks, such as Sprulac (Fairley · Cow and Gate) may be substituted

Details

Diet No 1 (on admission): 3 pints of cow's milk (or Benger's Food) daily, in 5 oz feeds, *2-hourly*, *small* quantity of toast with *taste only* of butter

Diet No. 2 3 pints of milk as above, rusks or toast in small quantity, sago 6 oz; liver soup 12 oz in 2 feeds of 6 oz each, one lightly boiled egg; weak tea 8 oz

Diet No 3 Breakfast – porridge, 1 egg, toast and weak tea; 11 a m, *½ pint warm milk*; lunch, liver soup 12 oz, minced chicken 6 oz, spinach 3 oz (or cauliflower 3 oz), sago or semolina 6 oz, baked apple or banana 6 oz; tea, toast, tea, sponge or Madiera cake, or digestive biscuit 3 oz; dinner, brain or sweetbread, 4 oz, apple, strawberries or raspberries 3 oz, arrowroot 8 oz.

(ii) MEAT DIET (Fairley)

Rump steak after removal of obvious fat is minced and lightly cooked in a pan in its own juices without the addition of cooking fat This mince constitutes the essential ingredient of the diet in the early stages Later the meat may be served unminced and fish and chicken may be substituted occasionally

Details

Diet No 1 (Calorie value = 770) 8 a m – underdone beef 3 oz, rusks ¾ oz, juice of ½ orange+glucose 2 drachms

12 noon – soup 4 oz+liver extract (= ⅛ lb), underdone beef 3 oz, rusks ¾ oz, juice of ½ orange+glucose 1 drachm.

6 p m – The same as at 12 noon

Protein· fat carbohydrate = 1 0, 0 3, 1 2

Note – When patients are very ill, two-hourly feeds of meat and beef-juice can be substituted

Diet No 2 (Calorie value = 1280) 8 a m – underdone beef 5 oz, rusks 1 oz, calves-foot jelly 2 oz, juice of 1 orange+glucose 2 drachms

12 noon – soup 4 oz+liver extract (= ⅛ lb), underdone beef 5 oz, rusks 1 oz, juice of 1 orange+glucose 2 drachms

4 p m – tea 10 oz, milk 2 oz

7 p m – The same as at 12 noon+calves-foot jelly 2 oz

Protein fat carbohydrate = 1 0, 0 3, 1 0

Diet No 3 (Calorie value = 1820) 6 a m – tea 10 oz, milk 2 oz

8 a m – underdone beef 6 oz, rusks 1½ oz, calves-foot jelly 2 oz, juice of 1 orange+glucose 2 drachms.

10 a m – 1 baked apple+custard 1 oz

12 noon – Soup 4 oz+liver extract (= ⅛ lb), underdone beef 6 oz, calves-foot jelly 2 oz, rusks 1½ oz, juice of 1 orange+glucose 2 drachms

4 p m – Tea 10 oz, milk 2 oz, 1 baked apple 1 oz+custard 1 oz

7 p m – The same as at 12 noon

Protein fat carbohydrate = 1 0 0 32 1 3

Diet No 4 (Calorie value = 2200)

6 a m – Tea 10 oz; milk 2 oz

8 a m – Underdone beef 7 oz, rusks 1½ oz; calves-foot jelly 2 oz, juice of 1 orange+glucose 2 drachms.

10 a m – 1 baked apple+custard 2 oz

12 noon – soup 5 oz+liver extract (= ⅛ lb), underdone beef 7 oz, calves-foot jelly 2 oz, rusks 3 oz, juice of 1 orange+glucose 2 drachms

4 p m – tea 10 oz, milk 2 oz, 1 baked apple + custard 3 oz.

7 p m – The same as at 12 noon, but only 1½ oz of rusks allowed
Protein fat carbohydrate = 1·0, 0·34, 1·3.

Diet No 5 (Calorie value = 3020). 6 a m. – tea 10 oz, milk 2 oz, glucose 2 drachms, rusks 1½ oz, butter 1 drachm, 1 scraped ripe apple or 1 fully ripe Canary banana (yellow ends).

8 a m – underdone beef 7 oz, rusks 3 oz, calves-foot jelly 2 oz, juice of 1 orange+glucose ½ oz, honey 2 drachms, butter 1 drachm

10 a m – 1 baked apple+custard 3 oz.

12 noon – soup 5 oz+liver extract (= ⅝ lb), underdone beef 7 oz, calves-foot jelly 2 oz, rusks 1½ oz, juice of 1 orange+glucose ½ oz.

4 p m – tea 10 oz, milk 2 oz, glucose 2 drachms, rusks 2 oz, baked apple 1 oz, custard 3 oz (egg boiled or poached sometimes substituted) honey 2 drachms

7 p m – The same as at 12 noon
Protein fat carbohydrate = 1·0, 0·36, 2·0

(III) MAINTENANCE DIET

After the patient has become stabilized on the top milk or meat diets, he should be gradually taught to find a suitable maintenance diet which can be given him in his home surroundings He must be persuaded to take an intelligent but not neurotic attitude towards food and find out for himself what suits him and what does not. He can eat meat, fish, poultry and most ordinary foods but must avoid certain articles, including twice cooked or fatty meat, fat fish such as salmon or herring, game; vegetable containing excess roughage, spiced foods and condiments, salad and other oils, fresh bread and carbohydrates such as sweets; alcohol and sweet drinks.

OTHER MEASURES

(a) *Liver Therapy*

The addition of liver or its extracts to the diet speeds up the process

which may be stopped in a few days with accompanying general improvement in gastrointestinal symptoms Vitamin deficiency signs also often respond quickly The effect on the blood picture in anaemic patients is much slower

These effects may be obtained in mild cases by giving lightly cooked liver, but in more severe cases extracts are administered orally or parenterally. Crude extracts are more effective than refined Refined extracts which are active in pernicious anaemia may be inactive in sprue.

intramuscular injection

In oral treatment, the extract is given in water or milk daily in large doses over a period of weeks. Parenteral injection should be given daily for the first two to three weeks, then once or twice weekly through treatment. The dosage varies from extract to extract but full dosage will be required. In the case of Hepatex, for instance, daily injections of 4 ml may be followed by weekly injections of 10 ml.

It is generally agreed that liver extracts contain certain beneficial substances in addition to the known protein and vitamin content. What the substances are has not been fully determined, but it is probable that both folic acid and vitamin B_{12} are among them, since in some cases dosage with these compounds may be successfully substituted for liver therapy.

(b) *Folic Acid*

Folic acid belongs to a group of substances known as pteroylglutamates, which are present in liver, crude liver extracts, dark green vegetables, kidney, beef and certain cereals. The pure substance is therapeutically active in megalocytic anaemias of the megaloblastic type.

Its effect in sprue varies. Sometimes it is dramatic. The patient gains weight rapidly, the blood picture improves, the response of the gastrointestinal symptoms, especially the diarrhoea, is spectacular and the deficiency signs clear quickly. The effect on the fat absorption defect is, however, minimal and relapse may occur even during treatment. In other cases, folic acid has little effect on the blood picture, but even in these cases some improvement in gastrointestinal symptoms is common.

Folic acid should be administered along with the graded diets referred to above, not as a substitute for them.

It may be given orally or parenterally. In severe cases 10 to 20 mgm may be given intramuscularly daily for the first fortnight of treatment followed by an oral maintenance dose of the same amount weekly which may be continued for months. Milder cases may be given the same dose orally twice weekly.

(c) *Vitamin B_{12}*

This may be given sometimes as a substitute for liver extract or folic acid. One of the many recognized preparations should be given as recommended by the manufacturers. It should be given only as an adjuvant to appropriate dieting.

(d) *Vitamins*

[illegible]

are Marmite and extracts of yeast. Their administration often brings about a rapid improvement especially in diarrhoea and dyspepsia

Nicotinic acid or amide and riboflavine are very effective in controlling the tongue and mouth lesions Vitamin C is rarely deficient, but it is advisable to see that this diet contains fresh fruit juice Fat soluble vitamins are not commonly deficient in sprue Where the *prothrombin index is low, large doses of vitamin K may be given orally* or smaller doses parenterally.

The administration of vitamins will not check the advance of the syndrome or improve the absorption defects. It must be regarded merely as an accessory to the basic dieting

Dosage· Nicotinic acid or amide· 50-200 mgm daily in divided doses orally or parenterally for a fortnight followed by a similar dose once or twice weekly if necessary for months.

Riboflavine. 3 to 5 mgm daily by mouth until the signs clear.

Combined vitamin treatment Nicotinic acid may cause unpleasant vascular flushing. The amide does not do this It may also unmask deficiencies in thiamin and riboflavine It is probably better therefore to give mixed vitamin therapy, at any rate after initial improvement has been obtained by the use of the pure substances. There are many excellent oral or parenteral proprietary preparations for this purpose.

(e) *Mineral Replacement*

As the patient improves under treatment mineral deficiencies tend to adjust themselves. In some cases, however, replacement may be an urgent necessity.

Calcium In cases with low plasma concentrations calcium can be given as soluble salts by mouth or, if necessary, intravenously. Calcium is best given as the lactate, grains 30, three times a day. Where there is severe steatorrhoea the dose may have to be increased because of the formation of soaps. Dosage with calcium salts often lessens the diarrhoea for this reason, and may be used for this purpose

Sodium chloride: In serious dehydration fluid and salt must be immediately replaced This will usually have to be carried out intravenously

Details of replacement, which are the same as those for other causes of mixed salt and water deficiency are given elsewhere (See p. 127)

In severely ill patients fluid and salt may be accepted orally, and stored in the intestine without absorption It is wise, therefore, to treat all dehydrated cases parenterally in the first instance

An intake/output fluid balance must be kept in all cases

juice after meals.

(f) *Transfusion*

Transfusion may be required in severely anaemic patients It is necessary if the red cell count is less than 1 5 million per cu mm Transfusion of a small amount of blood may occasionally stimulate blood regeneration in unresponsive cases

(g) *Control of Diarrhoea*

Calcium salts, as mentioned above, may lessen the diarrhoea and improve the appearance of the stool in patients in whom the fat absorption is especially poor and large amounts of split fat are being excreted

Insoluble sulphonamides and antibiotics are often effective in controlling the diarrhoea in early cases, especially those passing watery stools

Dosage Sulphaguanidine Initial dose of 7 gm, followed by 3 5 gm 4-hourly up to a total of 60 to 70 gms

TREATMENT OF 'SPRUE SYNDROME'

Early mild cases of the 'sprue syndrome' respond well to chemotherapy aimed at readjusting the intestinal flora Short courses of either insoluble sulphonamides, antibiotics or mixtures of these drugs are followed by rapid increase of weight and improvement in fat absorption, with disappearance of symptoms Recovery may be complete

More severe cases require treatment similar to that of tropical sprue

XXXII

TRACHOMA

DEFINITION

A GRANULOMATOUS viral conjunctivitis causing serious complications involving the cornea and eyelids.

DISTRIBUTION AND AETIOLOGY

Trachoma has a world wide distribution It is specially common in certain hot dry areas of the tropics and subtropics.

The causative agent is a large virus belonging to the pittacosis-lymphogranuloma group The disease has been successfully transmitted [illegible]

spread.

PATHOLOGY

The infection in trachoma primarily involves the conjunctival epithelium The more superficial cells change to pavement type, and may exfoliate, the deeper cells proliferate as ramifying columns into the [illegible]

scattered follicles In the later stages so-called trachoma bodies or granules develop, consisting of a central mass of mononuclear macrophages and large cells containing cytoplasmic inclusions, and a peripheral collection of lymphocytes Irregular scarring eventually develops, especially in the upper lid

Involvement of the cornea appears very early in the form of lymphocytic infiltration and vascularization nearly always in the upper limbus The pannus so produced extends and is often complicated by ulceration of the corneal epithelium

At any stage the picture may be complicated by the effects of secondary bacterial infection

CLINICAL PICTURE

The onset is usually insidious In experimental trachoma it may occur within a few days of inoculation of infective material

The first signs of the disease are often missed because they are so mild as to cause no appreciable symptoms. The earliest indication [illegible] follicles can be clearly seen against the hyperaemic background and after [illegible] such are not formed and the mucosa appears reddened and velvety This occurs especially in the presence of other bacterial conjunctival infection, and is usually accompanied by acute symptoms of irritation including some palpebral oedema, lachrymation and mucopurulent discharge

The inflammatory reaction invades the cornea in the earliest stages Infiltration with lymphocytes and increased vascularization of the conjunctiva superior to the cornea is followed by similar changes in the cornea itself and a pannus is formed in the upper limbus The symptoms and signs become more severe and the patient often now appears for the first time for treatment

The lesions develop especially in the upper lid, almost always in both eyes On inspection of the tarsal conjunctiva after eversion, pathognomonic small granules may be seen protruding above the general level of the surface. These measure a millimetre or more across They closely resemble boiled sago grains and contain mucoid material which can be easily squeezed out by pressure There may be only one or two or there may be large numbers There is usually an accompanying papillary hypertrophy which is displayed as a red rough or shaggy background almost invariably secondarily infected Symptoms are often severe The eyes itch and irritate There may be thick gluey or mucopurulent discharge Lachrymation and photophobia may be intense Repeated attacks of acute bacterial conjunctivitis often occur and exacerbate the condition In untreated cases corneal complications are very common. The pannus intensifies Small ulcerations appear at the advancing edge or within it The ulcers are small, shallow, only slightly infiltrated and very irritating and painful. They easily become secondarily infected and may lead to permanent corneal scarring and opacity

Trachoma tends to heal by scarring, leaving fine white cicatrices, mainly, in the upper lids just inside the lid margin and over the tarsal plate Scarring may be excessive in the region of the Meibomian glands and eventually leads to distortion of their orifices and to inversion of the edge of the lid (entropion) so that the eyelashes point inwards and rub against the cornea (trichiasis) These are common complications Where oedema of the lid is excessive (usually a sequel to heavy

secondary infection) the edge may evert rather than invert (ectropion). The lower border of the upper lid is frequently distorted

When pannus is severe the upper lid is often carried well down over the eye, giving the patient a sleepy appearance. This ptosis is a very characteristic clinical sign of the disease.

In the late stages of untreated trachoma the deformity of the lids, especially the upper, may be extreme. Damage to the cornea from pannus, ulceration, secondary infection and scarring may lead to permanent blindness.

DIAGNOSIS

Scrapings (stained with Giemsa or iodine) from early cases, but not always from later ones, may reveal the cytoplasmic inclusion bodies, which appear as red acidophilic granules against a circumscribed bluish background of inclusion material, the whole forming a small mass lying close to the nucleus and somewhat smaller than it. Similar inclusions are found in other conditions, including non-gonococcal conjunctivitis of infants and follicular conjunctivitis.

Clinical diagnosis in the early stages depends on inspection of the conjunctiva and the detection of characteristic follicles Early invasion of the cornea is important. Some authorities suggest that a clinical diagnosis should not be made unless pannus is present Appearance of sago granules is diagnostic. By this time pannus will be well developed.

TREATMENT

Control of secondary infection is essential in all cases In early cases frequent instillation of zinc sulphate solution is usually successful

There is some argument as to whether sulphonamides or antibiotics are specific or act mainly by control of secondary invaders Whatever the answer is, they are both highly successful in the treatment of even advanced trachoma and in preventing or controlling many of its complications.

Sulphonamides may be given in the usual doses orally Frequent local instillation of a 10 per cent solution of sodium sulphacetamide, every 2 or 3 hours, with liberal application of sulphacetamide ointment at night is more successful.

Improvement is often immediate and early cases may heal in 10 days to 2 or 3 weeks The average case responds well after several weeks. Treatment should be continued until corneal complications have settled.

Of the antibiotics, aureomycin and chloramphenicol appear to be the best. Some moderate success has been obtained with penicillin

Aureomycin. Local instillation 0 5 to 1 0 per cent borated salt solution every 3 or 4 hours during the day, 0 5 per cent anhydrous ointment at night

Oral administration 250 mgm every 4 hours on the first day, 250 mgm 6-hourly for the next 6 days

The response is very rapid and satisfactory Corneal complications heal rapidly Scarring is minimal after treatment, and cases have been followed for months without relapse

Chloramphenicol Local instillation 4 per cent solution every 3 or 4 hours.

Oral administration (with or without instillation) 3 gm on the first day in divided doses 3-hourly On the second to fourth days, 1 5 gm in divided doses 3-hourly

Children may be given 1 5 gm daily in divided doses for 4 days

A 2 0 per cent anhydrous Acromycin ointment is also effective

SCARRING AND DEFORMITY OF THE LIDS

XXXIII

TROPICAL EOSINOPHILIA

DEFINITION

TROPICAL pulmonary eosinophilia; eosinophilic lung; tropical eosinophilic asthma. An inclusive term for a condition of high eosinophilia associated with loss of weight, cough and pulmonary symptoms sometimes resembling asthma or tuberculosis and with peculiar radiographic pulmonary changes.

DISTRIBUTION

The disease occurs most commonly in India and Ceylon It has been recorded also in tropical Africa, the West Indies, northern South America, Burma, Siam, Malaya and the East Indies. Isolated cases have been reported from Korea and Australia

AETIOLOGY

The cause in some cases is unknown. It is probable that several entities may be included within the syndrome. Allergy is believed to be responsible for some cases, arising as the result of filarial or other helminthic infection, especially worms not fully adapted to man Some [illegible]

The condition is commoner in coastal regions than inland. There is no obvious seasonal incidence, although symptoms are sometimes exacerbated in wet or very hot weather

The disease is found in Indians more frequently than in other races Chinese are probably the next most commonly involved Europeans are affected less frequently

Sex and occupation do not seem to be important aetiological factors

The peak incidence in most regions is found in the age group 21-40 years. In some parts of southern India children are most frequently affected Cases have been recorded in subjects under 6 and over 60 years of age

Occasionally a series of cases may appear in one family

PATHOLOGY

Practically nothing is known of the morbid anatomy of the condition

The radiographic picture indicates that the lung changes resemble those of virus pneumonia

The only change in the blood cells is in the leucocytes There is a great increase in absolute numbers of eosinophils Other white cells are not affected Details are discussed below The erythrocyte sedimentation rate (ESR) is increased in the acute condition and restored after treatment Sternal marrow smears often show an increase in eosinophil elements which decrease slowly after treatment The Wasserman and Kahn reactions are negative

Smears of sputum show epithelial cells and eosinophils in clumps The bacteriological content is mixed and not specific Blood may be present Larvae of nematodes are found only exceptionally Mites, chiefly belonging to the family *Tyroglyphidae*, which are commonly associated with dust, debris and stored foods may be found in small numbers in the centrifuged deposit of sputum digested in 4 per cent sodium hydroxide

CLINICAL PICTURE

Tropical eosinophilia has been defined only over the last 20 years The importance of its recognition lies in its sometimes severely incapacitating effects, in the possibility of early relief with arsenicals, and in the frequent confusion between it and pulmonary tuberculosis, bronchial asthma and bronchiectasis

The clinical picture varies considerably

The pattern of the usual case includes cough, most frequent and severe at night and often appearing in paroxysms, with mucoid or mucopurulent sputum and sometimes blood, chest pain after coughing,

increase in hilar shadows, transverse striations and irregular mottling, commonly involving the lower lung fields and rarely affecting the apices

Clinical History By far the commonest complaint is coughing, which

Paroxysms are of considerable violence, lasting a few minutes to half an hour, often repeating several times during the night The patient is forced to sit up and his sleep is badly disturbed

There is considerable breathlessness after coughing and frequently a feeling of suffocation, accompanied by rapid panting respiration In many patients the breathing resembles that in asthma but bronchial spasm is not always present and the dyspnoea is not always expiratory

in type. In some, however, there is true bronchospasm leading to asthma *Status asthmaticus* has been reported

Most patients experience a sense of constriction about the chest during and for some time after the cough paroxysm. There may be dull aching pain over the front of the chest probably resulting from muscular overaction, especially of the accessory respiratory muscles Epigastric pain is commonly present during and for some time after the paroxysms of coughing

Sweating is frequent during and particularly after coughing.

In a few cases there may be no cough or other respiratory signs, the chief complaint being progressive fatigue and loss of weight.

Coughing is followed by expectoration of mucoid or mucopurulent sputum sometimes in considerable quantities. The sputum is often streaked with blood and occasionally small haemoptyses may occur and continue for several days

Chest Signs In about a quarter of cases there may be no obvious signs even when the clinical picture is severe Scattered sibilant or sonorous rhonchi may be heard over both lungs, there may be coarse basal crepitations Adventitious sounds are rarely heard in the apices The expiratory sound is usually prolonged Signs of emphysema are common

Pulmonary Radiographs In the active stage the hilar shadows are usually enlarged irregularly, with blurred outlines The lung fields are commonly crossed more or less transversely by fine irregular branching striations which are most evident in the mid- and basal zones

Mottling is present in most cases at some stage It is most prominent in the basal zone, sometimes the mid zone The mottled shadows appear as discrete soft rounded ill-defined spots varying from pin-head size up to 3 cm across They closely resemble the shadows of miliary tuberculosis but are not so sharply marked out and are much more regionally distributed

The radiological patterns are frequently bilateral and basal. Occasionally they may be unilateral and may occupy the infraclavicular *lung fields, closely resembling tuberculosis*

Mottling is not always present. On the other hand, it may be the only sign Patchy emphysematous changes occur in old standing cases, especially in the basal zones

The radiological shadows disappear quickly on treatment, i.e usually within a month They commonly reappear in relapses.

in early cases There may be shadows of large consolidations in rare cases, and sometimes thickening of the pleura, especially at the bases

THE BLOOD

White cell count The white count is invariably raised, due to a great increase in eosinophils The latter constitute 25 per cent or more of the total cells The other cells are present in normal numbers

Total white counts range between 10,000 and 100,000 cells per cu mm of which eosinophils may represent 25 to 80 per cent Common values for the total white count range from 15,000 to 35,000 cells per cu mm

In a given case the white count and the percentage of eosinophils fluctuate from time to time but it is an essential criterion of the diagnosis that the latter should always be of the order of 20 per cent or more

Intercurrent infection often reverses the picture, the polymorphs increasing and the eosinophils reducing After the infection the original picture returns

E S R The erythrocyte sedimentation rate is increased in most cases The actual figure varies from patient to patient and from time to time in the same patient It is often of the order of 20 to 60 mm per hour The rate returns slowly towards normal after treatment or spontaneous recovery

The E S R may be helpful in diagnosis For example, it is seldom raised in worm infestation or in allergic asthma, in both of which moderate eosinophilia occurs

General The patient is usually thin and somewhat emaciated Lack of sleep resulting from nocturnal paroxysms of coughing may cause great weariness and a desperate desire for rest

Acute cases may have mild fever which persists or appears irregularly throughout the illness They are often afebrile

There are no circulatory disturbances The heart is not dilated, and the pulse, which may be fast during the periods of coughing and breathlessness, is otherwise normal

Lymph glands, the spleen and the liver do not enlarge. In a few cases there may be a mild epididymitis

COURSE AND PROGNOSIS

The disease is not fatal It may last for years with alternating periods of remission and exacerbation As a rule the development of symptoms is gradual, and the full picture is not achieved for months or years Occasionally it may be rapid

Spontaneous recovery occurs as a rule after a few months or years Recurrences are rare after more than two years of quiescence

Response to treatment is usually excellent

DIAGNOSIS

Clinical diagnosis is often difficult The eosinophil count is usually conclusive The total number of eosinophils per cu mm should exceed

3000 The total white count should be not less than 10,000 cells per cu mm Figures of this order or higher in the presence of pulmonary history confirm the diagnosis. A white count of about 10,000 cells per cu mm and an eosinophilia of 10 to 12 per cent may be taken as usual for the local population concerned

[illegible]

Points of distinction are the presence of fine crepitations in the apices in tuberculosis and the tendency for eosinophilic lesions to affect the bases and leave the apices clear The chief criteria, however, are the absence of *M tuberculosis* in the sputum, the blood picture and response to therapy.

The radiographic picture often superficially resembles chronic bronchitis and sometimes bronchiectasis Here again the blood picture and clinical history are helpful

In allergic bronchial asthma and allied conditions the patient complains of expiratory dyspnoea and coughs after relief. In the eosinophilic case there is often no expiratory difficulty and the cough occurs during the paroxysms Where eosinophilia occurs in bronchial asthma, hay fever, etc., it is never of the order seen in eosinophilic cases The same is largely true of parasitic infections, which should be distinguished by discovery of the causative agent.

The radiographic picture may be mistaken for that of Loeffler's syndrome, which is characterized by a very high percentage of eosinophils in a relatively low total white count In this syndrome, however, the lung changes are transitory and there is inflammation of the upper respiratory tract

Where filarial infection is the basis of the syndrome, filarial skin reactions or test doses of hetrazan may indicate the aetiological factor (See p 89)

TREATMENT

Arsenical compounds may be specific Many cases respond rapidly to a single course of treatment. Arsenicals act either when given parenterally or orally. The best results are obtained by parenteral treatment, as follows

Novarsenobillon· 300 to 450 mgm given intravenously. Dose repeated at weekly intervals for 6 to 8 weeks

Acetylarsan: 3 to 5 cc intramuscularly once weekly for 6 to 8 weeks

In those cases arising from worm infections, hetrazan in standard dosage may lead to cure, after the usual initial severe allergic reaction, which can be controlled by antihistaminics (p 91)

Cases failing to respond to arsenicals may respond to aureomycin in the usual dosage, or continued for a longer period

EFFECT OF TREATMENT

In many cases the use of arsenicals produces rapid and permanent cure In others hetrazan or aureomycin may effect a cure.

In a few cases there may be exacerbation of symptoms with fever and increase in eosinophils after the first injection of arsenic Treatment should be continued in spite of this Very rarely fatal arsenical encephalopathy may develop, this is commoner after oral treatment

With successful treatment, there is an immediate fall of total white count largely due to reduction of eosinophil numbers which come to normal levels in the course of a month to 6 weeks. After treatment the white count is usually 10,000 to 15,000 per cu mm, eosinophils 10 to 15 per cent

The [illegible]
within [illegible]
import[illegible]
philia from that of all other conditions

Relapses with return of eosinophilia and radiographic pattern may occur after a full course of treatment and demand a further full course About 10 per cent of cases relapse, usually within two years of treatment Further therapy is required, preferably with a drug other than that originally used

XXXIV

TROPICAL MYOSITIS

DEFINITION

LOCALIZED inflammation and abscess formation in the muscles of the limbs and trunk.

DISTRIBUTION AND AETIOLOGY

The condition is found in many parts of the tropics, particularly in Africa, parts of South America, and Japan It has been not decided whether there is any one common causative agent.

The pus from the abscess is bacteriologically sterile in about 10 per cent of cases, in most it contains *Staphylococcus aureus* or streptococci Some cases may result from secondary infection of filarial abscesses or the lesions of tropical phlebitis or sickle anaemia. Secondary infection of extravasated blood following haemorrhage from injury or scurvy is sometimes thought to be responsible

In the regions in which it is found it occurs mainly in the native population or those of mixed blood, and only very rarely in Europeans

It may appear at any age but is most common in the second or third decade Men, especially agricultural workers, are more often affected than women

CLINICAL PICTURE

The commonest site of the lesions is in the lower limb (thighs, calves and buttocks). The arms, chest wall and abdominal wall may be affected in that order There is usually only one abscess. Sometimes, especially in staphylococcal infections, there may be several.

The lesion usually develops for a week or more before the symptoms become severe enough for the patient to seek advice. There may be a history of local trauma In some cases there may have been a short episode of local lymphangitis In some cases the history is much longer, the lesion developing slowly over some weeks.

In the average case the patient's general condition is good but he

In the majority of cases the lesion resolves without pointing or requiring surgical treatment In some untreated cases pus may be discharged and indolent sinuses left after healing Death may occur in rare instances from the toxaemic effects of infection

DIAGNOSIS

The causative factors concerned being largely unknown, the immediate diagnosis is simply that of a muscle abscess The aetiological factors involved, for example, phlebitis, haematoma in scurvy, filarial abscesses require general investigation Confusion may arise with osteomyelitis and arthritis

TREATMENT

The patient should be nursed in bed The affected part, if it is a limb, should be rested, if necessary in splints Ordinary analgesics may be administered for pain Local treatment includes fomentation and either aspiration or open incision, drainage and packing, if the general condition (for example high swinging fever and leucocytosis) demands interference As much as a pint may be removed from a large abscess Some authorities claim that aspiration is preferable to open incision Sulphonamides have their advocates Sulphathiazole or sulphadiazine 1 5 gm three times a day for 1 week are successful in some cases

Antibiotics may be exhibited with effect in some cases, especially where the infective agent is staphylococcus Aureomycin is likely to be more effective than penicillin

Hetrazan in the usual doses may be given after the control of the secondary infection if there is reason to suspect filarial infection

XXXV

TROPICAL PHLEBITIS

DEFINITION

A PRIMARY thrombophlebitis occurring in Africa, possibly of viral origin.

DISTRIBUTION AND AETIOLOGY

The condition was first described in East Africa, but is now known to have a widespread distribution throughout Africa

It occurs most often in otherwise healthy young male adults. There is no obvious occupational incidence. It is predominantly a disease of Africans, but has been reported in a few Europeans working in Africa

There is no seasonal incidence, but outbreaks, resembling small 'epidemics', occur from time to time.

It is believed on the grounds of the pathology and clinical appearance, that the causative agent may be a filterable virus; it has been suggested that in some cases it may be syringe transmitted.

PATHOLOGY

There is gross interruption of the vessel wall in all its divisions by granulation tissue containing multitudes of newly formed blood vessels, fibroblasts, endothelioid cells, giant cells and macrophages, some of which contain so-called cytoplasmic inclusion bodies The lesion is especially prominent in the media and extending well into the connective tissue surrounding the vessel The vasa vasorum are not cuffed with round cells In the immediate vicinity of the lesion the thrombus is firmly adherent to the vessel wall Distally there may be obvious secondary thrombosis In the later stages there are usually considerable organization and recanalization of the clots

CLINICAL PICTURE

The condition occurs in two main forms, differing only in severity, namely, *phlebitis major* and *phlebitis minor*

In the former, large veins are involved and the general reaction is severe In the latter small veins are involved and the general reaction is mild or negligible

PHLEBITIS MAJOR

This condition is acute and usually non-recurrent. It may affect both superficial and deep vessels There may be a day or so of prodromal malaise The syndrome commences suddenly with intense pain in the affected area Acute tenderness along the course of the affected vessel is common from the outset and there may be some protective spasm of regional muscles Within a few hours local swelling occurs and the tenderness and pain may increase and make examination very difficult The distal veins become engorged and oedema may develop, especially if a limb vein is affected The onset is accompanied by fever and constitutional signs The temperature varies considerably In some cases it is high, especially when very large vessels are involved In the normal course of events the temperature returns to normal and the local signs subside in a few days Occasionally in severe cases, especially when there is secondary thrombosis, the temperature may remain elevated for 2 to 3 weeks

Palpation of the inflamed vessel is usually possible only after the sub-

which, because of the extensive local connective tissue reaction is often thickened considerably more than would be expected if the lesion were confined entirely to the vessel wall There may be one or more swellings on the vein, measuring an inch or two in length

More than one vessel may be involved

Healing is slow, but in uncomplicated cases the swelling eventually disappears and circulation is ultimately restored Suppuration does not usually occur, but it is possible that phlebitis may explain occasional cases of tropical myositis

The local picture is complicated by the vascular effects of obstruction to circulation These effects depend on the vessel affected In the leg the femoral vein is often involved The leg becomes oedematous, the oedema subsiding slowly The distal vessels become congested early and some form of collateral circulation may eventually be established

Any large veins may be affected, including the superior or inferior vena cava In the former case both arms and the neck and face become oedematous and congested In the latter, oedema of both legs, the pelvis and lower abdomen may develop Thrombosis may also occur in the venous sinuses of the skull, or in the mesenteric veins In the latter case there develops an acute abdominal crisis with severe epigastric pain, vomiting and shock, blood may be passed per rectum

It is believed that the splenic vein is involved occasionally leading to multiple or total infarction, this may be a cause of primary splenic abscess It has been suggested that tropical phlebitis may be responsible

for some cases of gangrene in the extremities. Secondary embolus is very rare. Oedema may be the only presenting sign after deep thrombosis.

The prognosis depends mainly on the vessels affected. Thrombosis of the vena cava, or visceral veins, may be fatal.

PHLEBITIS MINOR

Mild cases may exhibit sudden local pain, tenderness and oedema without fever or other constitutional signs The patient may notice painful lumps in the extremities These are found to be related to veins. There may be several along the line of a single vessel, and a number of veins may be involved. The swellings are firm, tender, up to two inches in diameter They usually subside completely in a few weeks There may or may not be accompanying distal congestion and oedema.

Outbreaks of acute cervical phlebitis accompanied by constitutional symptoms have been described The patients may develop stiff neck and slight fever, sometimes with no obvious signs suggesting local thrombosis They may go on to recovery, relapse or subsequently develop thrombophlebitis elsewhere. During these so-called 'epidemics' some subjects develop fever only.

DIAGNOSIS

The clinical condition in a case in which a superficial vessel is involved is usually easy to diagnose When the vessels are deep the diagnosis has to be considered along with many other conditions and may be very difficult Associated arteries may occasionally be involved, but the very acute local changes accompanied by fever and constitutional signs will usually distinguish the condition from other forms of thrombophlebitis such as Buerger's disease Tropical myositis may be difficult to distinguish when the phlebitis occurs in the deeper small veins, especially those of the neck Local lymph gland enlargement must be excluded

TREATMENT

There is no known specific treatment Local treatment consists of rest and elevation where possible. Sulphonamides or antibiotics do not seem to affect the clinical course except where secondary infection has occurred Anticoagulants such as heparin may be indicated but there is no record of their use

XXXVI

TROPICAL ULCER

DEFINITION

SUPERFICIAL ulceration of uncertain aetiology found extensively in the tropics and usually associated with the presence of *Bacillus fusiformis* and *Treponema vincenti*

DISTRIBUTION

Tropical ulcer is common in certain districts of tropical South America, Central America, the West Indies, Africa, India (Naga sore), Assam, Ceylon, Indo-China, south China, Malaya, Indonesia, the Philippines, Melanesia, New Guinea, Northern Australia, the Solomon and other Islands

It has occurred in 'epidemics' at various times in North Africa, Melanesia and Assam

AETIOLOGY

The aetiological factors concerned in the appearance of tropical ulcers have been summarized in the phrase 'filth, food, friction and fuso-spirillosis' To these must be added local trauma

Tropical ulcer is seen most frequently in low lying, hot, moist regions, it may occur, however, at levels as high as 6000 feet above sea level It is particularly common in open air workers whose work is sweaty, and who are exposed to local injury, especially about the legs It is more common in males than in females, and in adolescents and young adults than in children or the aged

It is associated with filthy overcrowded living conditions and appears particularly in those who wear little clothing and go barefoot Malnutrition and dietary deficiencies, especially of protein, predispose to ulceration Some authors have incriminated avitaminosis A or avitaminosis C, while there is some evidence in favour of the former it has been shown recently that administration of vitamin C is without effect Concomitant debilitating diseases, especially malaria are frequently present

It is not known how the ulceration is established but it is generally accepted that direct contagion from ulcer to skin is important It is possible that flies may spread the condition by passing from feeding on an active ulcer to bites, cuts and abrasions on the new victim Local

injuries, especially cuts and abrasions, are probably necessary for successful inoculation Ulcers have been observed in parts of the body which have been pricked or cut by instruments used for the surgical excision of known lesions.

In freshly developing ulcers two organisms are practically always present, i e *B fusiformis* and *Treponema vincenti*. It is not certain whether these are true causal agents or secondary invaders, but their association with this form of ulcer is so close as to permit the working hypothesis that they are concerned in its genesis. Other organisms including various pyogenic cocci are also present, but inconstantly and in relatively small numbers

Bacillus fusiformis is a sausage shaped straight or curved rod of variable size The ends are tapered and in stained preparations, the body is characteristically banded or beaded The organism is an obligatory anaerobe It is usually nonmotile, but some motile strains have been observed It is gram positive, but decolorized by long exposure to alcohol It is found in enormous numbers in active ulcers. It is less *prominent in and may be absent from more established lesions* It disappears during healing and may return in a relapse

Treponema vincenti is an actively motile anaerobic treponema with several loose spirals It is found in the necrotic material covering the ulcer surface and for some depth in the granulation tissue beneath It is believed to be the same organism as that found in Vincent's stomatitis

Both *B fusiformis* and *T vincenti* are found in the buccal cavity under normal conditions It is not known whether spread from the mouth is [illegible]

fresh ulceration to both animals and man Intradermal injection of cultures of either organism separately does not readily produce ulcers, although mixed injection is sometimes successful Filtrates from ulcer slough or tissue are non-infective.

Transmission by means of injection of material from fresh ulcers is usually successful only if the recipient tissues are bruised or injured in some way

The role of other organisms including the pyogenic cocci is also uncertain It is believed that they may be important pathogenic agents in some cases, secondary invaders in others

PATHOLOGY

The active ulcer· Examination of the slough or of the scrapings from the granulation tissue beneath will reveal multitudes of both *B. fusi-*

formis and *T vincenti*. There will usually also be staphylococci and streptococci, but in much smaller numbers.

At the growing edges of the ulcer the epithelium is raised and thickened and deep papillary processes project into the corium The surrounding skin and corium is often oedematous and irregularly infiltrated with polymorphs

In the ulcerated area the surface tissues undergo coagulative necrosis and merge with a loose pseudomembrane consisting largely of fibrin, necrotic cells, masses of fusiform bacilli, and spirochaetes

The deeper tissue is infiltrated with lymphocytic and plasma cells and with foci of polymorphs The lesion extends into the surrounding connective tissues and there is usually a considerable mobilization of fibroblasts beneath the ulcerated area In severe rapidly progressive cases the deeper underlying tissues may be affected, especially bone, which may become necrotic Muscle is usually not attacked

In rare cases large blood vessels may be eroded

The established ulcer. After its early rapid growth the ulcer tends to remain more or less stationary, sometimes for many years The acute inflammatory reaction subsides and the base becomes filled with indolent granulation tissue New epithelium is formed at the periphery and grows slowly in towards the centre of the ulcer Hypertrophy and downgrowth of the epithelium at the edges is prominent In long-standing ulcers there is often extensive dense fibrosis in the tissues beneath and proximal to the ulcer

Healing eventually occurs and the ulcerated area becomes thinly epithelialized from the edges inwards The epithelium over the healed ulcer is often thin and easily damaged and relapses are common In long-standing lesions or in those in which there has been extensive necrosis healing may occur with gross scarring

Carcinomatous changes are common in long-standing indolent ulcers

CLINICAL PICTURE

Tropical ulcer appears most frequently on exposed parts of the limbs and body. It does not appear on the face It is commonest on the lower third of the leg, involving the ankle or dorsum of the foot, and sometimes the phalanges It also occurs frequently on the arms and fingers It is believed to arise as a rule in the region of bruising, cuts, abrasions, bites and other damage to the skin and subcutaneous tissues

There is usually only one ulcer at a time in a given patient Occasionally there may be a group suggesting autoinfection Relapse of ulceration is fairly common in the scars of old ulcers. No immunity is

injuries, especially cuts and abrasions, are probably necessary for successful inoculation. Ulcers have been observed in parts of the body which have been pricked or cut by instruments used for the surgical excision of known lesions

In freshly developing ulcers two organisms are practically always present, i.e *B fusiformis* and *Treponema vincenti*. It is not certain whether these are true causal agents or secondary invaders, but their association with this form of ulcer is so close as to permit the working hypothesis that they are concerned in its genesis. Other organisms including various pyogenic cocci are also present, but inconstantly and in relatively small numbers.

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Both *B fusiformis* and *T vincenti* are found in the buccal cavity under normal conditions It is not known whether spread from the mouth is concerned in any way with the pathogenesis of ulceration.

There is mounting experimental evidence indicating that material from ulcers containing both these organisms is capable of transmitting fresh ulceration to both animals and man Intradermal injection of cultures of either organism separately does not readily produce ulcers, although mixed injection is sometimes successful Filtrates from ulcer slough or tissue are non-infective

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PATHOLOGY

The active ulcer· Examination of the slough or of the scrapings from the granulation tissue beneath will reveal multitudes of both *B fusi-*

After a variable period, sometimes of years, the ulcer heals Epithelium grows in from the edges, and in the absence of heavy secondary infection may remain thin and delicate, so that further ulceration may result from trauma. Healing is not always complete Parts of the original ulcerated area may be covered with epithelium while other parts remain florid and active or are penetrated by discharging sinuses, especially if bone is involved Where there has been massive formation of deep fibrous tissue there is usually notable scarring and deformity Serious incapacity may result from the involvement of joints and subsequent ankylosis

The majority of cases are ambulant throughout Some general reaction including fever may accompany the developing stages of the ulcer, but on the whole the general effects are much less evident than might be expected from the appearance of the ulceration

There is no leucocytosis unless from other causes Some patients may show a relative lymphocytosis

Even in the acute stages local lymphangitis and lymphadenitis are uncommon, except when there is obvious secondary infection Local gland abscesses practically never occur and generalized septicaemia is very rare

The active ulcer is sensitive to pressure, the surrounds are itchy and may become secondarily infected by scratching As the ulcer becomes more established local tenderness and pain tend to become less pronounced, and may be absent Some depigmentation often occurs after healing

DIAGNOSIS

The existence of severe usually very chronic local ulceration without pronounced general symptoms is suggestive of tropical ulcer The appearance of the ulcer, with raised edges and a covering of grey bloody pseudomembrane is usually diagnostic Examination of the slough usually reveals an enormous variety of organisms including *B fusiformis* and *T. vincenti* The latter are present in practically all fresh ulcers and in many established lesions Preparations for examination should be made from the ulcerated surface after removal of the slough with saline or dry gauze Organisms are often found deep in the ulcerated tissues *T vincenti* is conveniently observed with dark ground illumination in wet preparations It stains well with Gram s stain or methylene blue and best with Giemsa

Other ulcerative conditions may have to be excluded Desert sore, cutaneous diphtheria, leishmaniasis and mycoses should be identified by examination, and are usually accompanied by other evidence of the disease Syphilis produces serpiginous penetrating irregular ulcers in which *B fusiform* is usually absent, there is likely to be other evidence

produced, fresh ulcers may develop in other parts of the body after the healing of an ulcer

Opportunities for watching the development of tropical ulcer are rare, since the patient usually seeks advice for the first time long after the ulcer has developed. In those cases which have been observed, however, and in experimental inoculation the lesion begins as a vesicle, which ruptures and leaves an ulcerating sloughing surface, or as a papule which enlarges rapidly, becomes inflamed and breaks down into ulceration

The active ulcer once formed spreads rapidly. It may measure two or more inches across in a few weeks, but it is commonly smaller It is very itchy and sensitive in this stage, causing considerable pain and annoyance.



FIG 50 Tropical Ulcer
[Courtesy of Dr H Peaston]

The skin near the lesion is swollen, reddened and oedematous The margin is slightly raised and the edges, which sometimes may be a little undermined, slope sharply down to the ulcerated surface The surface is covered with a foul smelling, grey-green, sometimes bloody slough forming a false membrane, attached firmly to the underlying tissues

The ulcer may stop growing in a few weeks, or may continue to spread slowly in width and depth, coming to involve surrounding and underlying tissue In the chronic stage the edge is pale, heaped up and hard, forming a raised ring round the ulcerated area The base is comprised of firm, pale, granulomatous tissue which does not bleed easily, and is free from slough

flavine 1 in 1000, alternating with bland ointment dressings at night, is also sometimes successful

Local applications of neosalvarsan (3 per cent) alternating with antiseptic dressings, and accompanied by intravenous arsenical therapy have been recommended by some workers

When healing has commenced after any of the above, a bland ointment such as zinc and castor oil or boric acid should be substituted and continued until epithelialization is complete

The rate of healing is roughly proportional to the size of the ulcer Healing usually takes some weeks

Occlusive therapy such as described below for the treatment of chronic ulcers has also proved successful in early cases

Sulphonamides given orally may be successful in some cases

Recent work indicates that the best treatment may be the oral administration of antibiotics, combined with local bland or antiseptic dressings

The combination of penicillin intramuscularly and applied locally has proved successful Aureomycin and chloramphenicol are also effective and have the great advantage of being administered orally The following dosage regimes have proved highly successful

Dosage

Aureomycin hydrochloride 2 capsules of 250 mgm three times a day for two successive days

Chloramphenicol 2 capsules of 250 mgm three times a day for 7 days

With these antibiotics healing begins in a few days and proceeds rapidly Relapse is said to be uncommon

The advantages of antibiotic treatment in mass campaign are obvious

THE CHRONIC ULCER

The established ulcer is indolent and may respond poorly to local treatment, oral sulphonamides or penicillin and other antibiotics A few cases have been successfully treated with aureomycin and chloramphenicol, as above

One of the most satisfactory methods of dealing with indolent chronic ulcers of the leg is the occlusive technique, which may also be successfully employed in early cases One of the great advantages of this method is that the patient is kept ambulatory and long periods of enforced rest are avoided

CONCLUSIVE TECHNIQUES

(1) *Adhesive tape* The whole leg below the knee is shaved, washed and dried The ulcer is cleaned and covered with gauze

of infection, including a positive Wassermann reaction This reaction is negative in tropical ulcer. The primary lesion of yaws may be confused occasionally, but it is slower in development, the surface of the ulcer is *different, being pale and shot with strands of epithelial tissue*, and without the characteristic slough; the Wassermann reaction is positive. The multiple lesions of secondary yaws should present no difficulty. Tertiary yaws ulcers are irregular, less well defined and have not the characteristic bacterial content.

Ulceration arising from varicose veins in the leg is uncommon in the tropics The pathogenesis of such ulcers should be obvious on inspection

TREATMENT AND CONTROL

Careful attention to local cuts and abrasions will greatly reduce the incidence of tropical ulcer in a population, especially in labour personnel

Whenever possible the affected part should be rested If the ulcer is on the leg, the limb should be elevated

The patient should be given a well-balanced diet containing adequate protein, and intercurrent infections, especially malaria, should be *treated*.

Removal of the patient from tropical to temperate surroundings is often followed by rapid healing.

TREATMENT OF THE ULCER

Many methods of local treatment have been recommended, most of which are fairly successful in early cases, but less so in long standing ulcers.

The early growing sloughing ulcer responds better to treatment than the *later more chronic stages*.

THE EARLY ULCER

Before any local application is made the ulcer should be thoroughly cleaned and as much of the necrotic material as possible removed This is best done mechanically with soap and water Gauze soaked in peroxide may be used to loosen adherent slough. In difficult cases gauze compresses of saturated magnesium sulphate or copper sulphate (1 in 200) may be applied daily until the slough separates These may be painful.

When the ulcer is clean, gauze dressings soaked in various substances may be applied daily, or the surface may be dusted with sulphonamide [illegible] employed as [illegible] iodo- [illegible] [illegible]IPP), [illegible] acri-

XXXVII

TRYPANOSOMIASES

AFRICAN TRYPANOSOMIASIS

DEFINITION

SLEEPING sickness A condition caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense* transmitted by *Glossina* (tsetse) flies The trypanosomes give rise to two distinct clinical entities, gambiense and rhodesiense trypanosomiasis

Gambiense trypanosomiasis develops slowly and is characterized by weakness, wasting, lethargy, fever, lymph-glandular enlargement, and eventual involvement of the central nervous system Rhodesiense trypanosomiasis develops more rapidly, glandular enlargement is uncommon and death may occur before the central nervous system is seriously involved

DISTRIBUTION

Trypanosomiasis occurs within a wide belt of territory in Africa lying between latitudes 10 N and 25 S stretching from Senegal and southern Sudan in the north to Angola and Portuguese East Africa in the south The distribution inside this area is patchy Regions of very high endemicity occur in French Guinea, British West Africa and the Belgian Congo

Gambiense trypanosomiasis is much more widely distributed than rhodesiense, which is largely limited to areas in East Africa, including Tanganyika, Uganda and Rhodesia Neither is found at elevations beyond 7000 feet above sea level

Epidemics may arise occasionally as the result of spread of infection from endemic to previously uninfected areas There are many historical examples of such new distribution of the disease

AETIOLOGY

CAUSATIVE ORGANISM

Trypanosomes are protozoa belonging to the family *Trypanosomidae* They undergo metacyclic development in the intermediate insect host In the human host the metacyclic forms are converted into trypanosomes which divide by longitudinal fission

In man *T gambiense* and *T rhodesiense* are morphologically identical. In the blood and tissue fluids, they appear as thin slender flagellates,

much discharge.

Intravenous arsenicals, intramuscular penicillin or oral aureomycin therapy may be combined with this local treatment.

Healing takes some weeks

(ii) *Plaster* The ulcer is cleaned or scraped, washed and powdered with sulphonamide powder. It is then covered with a single layer of sterile gauze cut to the shape and size of the ulcer. Over this is laid a larger layer of gauze smeared with sterile petroleum jelly or BIPP, so that the ulcer is covered for several inches all round A 3-inch plaster bandage is then applied Alternatively some form of elastic sticking plaster-bandage may be used

The patient is encouraged to return to work, and is told to report at regular intervals. Secretion that oozes through the plaster is removed with soap and water and the casing is left untouched for a month or more if possible before being removed and replaced.

Healing should take place in about 3 months

Radical Treatment may be needed in a few cases, especially when the underlying bone is affected. Cauterization or total excision followed by skin grafting has been employed with some success Resort to such methods should be made only after the simple procedures have been given an extended trial.

They need shade and moisture and are found in the region of shady trees and scrub near lakes and rivers The optimal temperature for their breeding is 75° to 85° F Hot dry conditions are unfavourable Flies do not normally travel widely from their breeding grounds The distribution differs with the species Thus *G palpalis* and *G. tachinoides* are very dependent on shade and moisture and are never found far from them Their distribution and that of gambiense infection which they carry may thus be locally limited *G morsitans* is hardier and less dependent on moisture and consequently ranges much wider

The flies bite by daylight Both sexes carry the infection They are attracted by moving objects and the disease may be spread by the carriage of flies from one area to another in motor cars and trains

Glossina flies produce single living larvae Their numbers are thus relatively limited The infection is not transmitted to the fly's offspring

TRANSMISSION

[illegible]

of infective blood on the biting parts of other flies, including *Tabanus* and *Stomoxys*

Transmission in a given area depends on man-fly contact It should be appreciated that man-fly contact may be of high degree even when the fly is scanty There must be suitable vectors in sufficient numbers, reservoirs of infection and non-immune human recipients In some regions it is believed that certain wild or domestic animals, notably the large antelope, may act as reservoirs of infective trypanosomes In general, however, the only reservoir of importance is man

All ages and either sex may be infected if exposed to the same conditions In many districts, however, the disease may predominate in one sex because of its particular occupation For example, fishing may lead to much greater exposure to infection

The European is likely to be affected more severely than the African The native population may acquire some form of resistance to infection with local strains of trypanosomes Resistance is more prominent after spontaneous recovery than after chemotherapeutic interference Its nature has not been defined

PATHOLOGY

In gambiense trypanosomiasis pathological changes develop at the site of the injection of the parasite, in the blood stream, in the lymphatic and serous tissues, in certain visceral organs including the heart, and, at a later stage, in the central nervous system especially the brain and

Leishman preparations the cytoplasm stains blue, there is a large oval centrally placed reddish nucleus; and a posteriorly placed kinetoplast In the short stumpy forms the nucleus may lie posteriorly. The undulating membrane projects beyond the anterior end of the body as a free flagellum (See Figure) In some individual parasites the flagellum may be absent The organisms are free moving.



FIG. 51
Trypanosoma gambiense and red cell
[From E. Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

They may be found at various stages of the disease, in the plasma, lymph and cerebrospinal fluid and in tissue spaces, for example, in the heart and brain.

Although morphologically indistinguishable *T. gambiense* and *T rhodesiense* cause clinically different diseases in man and are commonly transmitted by different species of glossina fly They are thus conveniently considered as distinct. It is believed by some that they are in fact identical and are the same as *T brucei* which infects herbivorous animals

Occasional human infections with other trypanosomes, for example, *T rangeli*, have been recorded

LIFE CYCLE IN THE FLY

When ingested by the right species of glossina fly trypanosomes

into the human tissues at biting

The fly becomes infective 18 to 34 days after feeding on blood containing trypanosomes.

THE VECTOR

A limited number of species of glossina fly is known to transmit trypanosomiasis

The most important species are· *G palpalis*, *G pallidipes*, *G. tachinoides* and *G. morsitans*

All will transmit *T. gambiense*, *G morsitans* is the principal vector of *T. rhodesiense*

Other flies may be of local importance, for example, *G swynnertoni*

Glossina flies have very special requirements for their multiplication

'nests' of trypanosomes, often surrounded by small glial cells, forming granulomata

The choroid plexus is often severely congested and infiltrated with lymphocytes It may harbour large numbers of trypanosomes in active stages of division

Scattered irregularly through the brain substance and especially near the infiltrated blood vessels there occur large eosinophilic mononuclear cells with eccentric nuclei known as morular cells (of Mott) These are believed to be macrophages There are frequently similar but less clearly developed changes in the upper reaches of the cord

The Cerebrospinal Fluid Changes in the spinal fluid occur early The pressure is moderately raised and the numbers of cells increased, the cells are chiefly lymphocytes Occasionally plasma cells, eosinophils and morular cells may be present The fluid is clear as a rule but sometimes the cellular content may be high enough to produce some milkiness

It early contains protein, chiefly globulin, the concentration of which increases as the disease progresses With the rise in protein, which may reach 100 mgm or more per 100 cc, there is a coincident fall in chloride and glucose

The colloid gold curve is of the tabetic type The G P I curve is seen only in very advanced cases

Trypanosomes are commonly but not invariably present in the late stages

CLINICAL PICTURE GAMBIENSE TRYPANOSOMIASIS

Gambiense infection may take the classical form but in populations of endemic areas it is often clinically mild, although it may end fatally by sudden exacerbation Fulminating cases resembling rhodesiense infection may also appear in which the cerebrospinal system is affected early, or there may be acute severe septicaemia, and death within a few weeks or months from the onset

The description of the disease that follows will concern first, the classical form, and second, the mild or apparently mild forms

CLASSICAL GAMBIENSE TRYPANOSOMIASIS

The classical picture of trypanosomiasis can be divided into several stages First, there is the tumour at the site of the bite Then follows the stage of invasion, starting as a septicaemia succeeded after a variable interval by invasion of the lymph glands This in turn is followed by nervous system involvement

The progress of the disease occupies anything from nine months to three years or more from the first appearance of symptoms

The Bite Reaction A red swelling, sometimes capped by a wheal, may

to some extent the cord with accompanying changes in the cerebrospinal fluid.

In rhodesiense trypanosomiasis the pathology is essentially the same but involvement of lymphatic glands is much less common and by the time of death the involvement of the central nervous system is frequently not as fully advanced as in gambiense infection In rhodesiense infections, serous effusions are more common and lesions in the heart more frequent and severe.

In both infections the development of the disease in the late stages is often complicated by emaciation, malnutrition and food and mineral deficiencies. Malaria and other infections also often complicate the pathological picture.

THE PATHOLOGY OF GAMBIENSE TRYPANOSOMIASIS

In what follows the pathological changes seen in gambiense infection are described. Points of difference in rhodesiense infection are mentioned in the section on that disease

Local reaction The pathological changes at the point of biting develop very early A firm tender reddened nodule may develop in the course of a few days composed of tissue infiltrated with lymphocytes and plasma cells and containing rapidly dividing trypanosomes; the smaller blood vessels are often cuffed with small round cells

Lymph glands. The enlarged glands contain large numbers of parasites developing in the sinuses, which are packed with round cells and macrophages There is a general proliferation of the lymphatic tissue, oedema and vascular congestion

Eventually the inflammatory reaction subsides and is replaced by fibrosis which is assisted by an obliterating endarteritis of the smaller vessels Perivascular infiltration may be pronounced. Trypanosomes are practically never found in this stage.

The brain tissue is oedematous in some cases, with flattening of the convolutions. The lesions are most pronounced in the pia mater. The basic change is a meningo-encephalitis in which perivascular cuffing with round cells and microglial cells is often pronounced There may be scattered minute haemorrhages. Changes in the blood vessels are independent of the local presence of parasites

Occasionally there may be some endarteritis of the smaller vessels Neuronal changes are late and secondary They are rarely severe In the substance of the brain, especially in the cerebral cortex and in the frontal lobe, the pons and the medulla, there may be accumulations or



FIG 52 Trypanosomiasis rash
[Courtesy *Annals of Tropical Medicine and Parasitology*, Liverpool]

appear within a few minutes of the bite. This subsides in a few hours and may be followed in about a week by a firm, tender, slightly reddened or violet nodule, over which the skin may be oedematous This tumour may become as much as an inch in length, raised above the surface and painful, or itchy. It is sometimes surrounded by a diffuse erythematous plaque-like area. Scratching may lead to ulceration and secondary infection; pus is not produced otherwise The ulcerated lesion is often referred to as a 'chancre'. The acute reaction commonly lasts only a few days; swelling may persist for two to three weeks, but subsides within a week. Fluid aspirated from it contains *actively dividing trypanosomes*. Further development of the infection can be stopped at this stage with suitable drugs The bite tumour is more often seen in Europeans than in natives of the endemic areas It is not usually associated with any general reaction.

THE STAGE OF INVASION

Incubation period In those few cases in which it has been possible to estimate the time elapsing between the infection and the appearance of symptoms the incubation period varies from 10 days to 3 weeks It may be very much longer Two or more years may elapse between the bite or a visit to an endemic area and the appearance of symptoms

Onset The attack starts with fever accompanied by malaise, lassitude, insomnia, and headache. The latter is the commonest of all early symptoms and the most persistent. Trypanosomes appear in identifiable numbers in the peripheral blood.

The Fever The fever may occasionally start with a rigor. It is irregular in intensity and duration, usually highest in the evening There may be severe sweating, especially at night. The initial fever seldom lasts more than a few days. It is followed by an apyrexial interval of variable length, usually some weeks.

Pyrexial and apyrexial periods succeed one another at irregular intervals for months, the fever eventually subsiding completely or becoming low grade and 'grumbling'.

The fever is invariably accompanied by a fast pulse, which persists into the apyrexial periods and sometimes throughout the disease Prolonged tachycardia may be easily brought on by exercise or excitement. The respiratory rate during the fever is high; anorexia is common and there may be some nausea and vomiting The urine frequently contains a small quantity of protein in the febrile period: sometimes this persists There may also be casts.

Rash: A rash may appear soon after the onset of fever. It is usually found on the trunk, especially the chest and back, but may appear on the face and limbs The eruption develops as irregular or circinate areas of transient erythema, with indistinct margins and a clear centre,

Lassitude and asthenia develop progessively as the disease advances The patient often becomes drowsy during the day and unable to sleep at night The appetite is not usually affected, but malnutrition is common in the more advanced stage, when the 'sleeping' patient may have to be roused to take food

THE STAGE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT

The clinical picture results from a continuous process of infection which eventually leads to a fully developed meningo-encephalitis and which frequently gives some indications of central nervous involve-



FIG 53 Early gambiense trypanosomiasis Falling asleep during feeding

ment at an early stage Central nervous system lesions usually predominate in the late stages of the disease, and may appear sufficiently distinctive to constitute a separate phase of the disease, known as 'sleeping sickness', which commonly develops six months to a year after the onset

The first indications of the development of central nervous system changes are often to be seen in exacerbation of already existing symptoms, particularly lassitude and apathy, which become progressively

often giving an annular appearance. Individual patches vary in size they may be several inches across. Sometimes the affected skin i oedematous and may be very itchy Fading occurs in a few hours there is no desquamation. The rash appears at irregular intervals I may sometimes be brought out by heat, e g after a hot bath. It i difficult to see on a coloured skin.

Oedema· Some cases may develop scattered areas of firm subcutaneou oedema, localized commonly in the eyelids, the sheath of the penis, o in the ankles, hands and feet. The oedema in a particular area may subside in a few days or weeks Several regions may be affected simultaneously or in succession.

In the course of the first few weeks of the disease a generalized puffi ness of the face usually develops, which gives the features a rather inane chubby expression

Involvement of lymph glands This usually occurs early and may be the first sign of the disease The distribution of enlarged glands is roughly symmetrical. Any gland may be involved Enlargement is often most obvious in the posterior cervical region (Winterbottom's sign) The affected glands are moderately enlarged and firm, they may continue to enlarge for months or years, tending to become softer as they get larger They often appear as obvious discrete tumours, unattached to the skin Eventually fibrosis takes place and the gland becomes a small hard discrete mass

Glands suppurate only if secondarily infected, as they may be following interference by native doctors

Glandular enlargement occurs in the majority of cases; it may occasionally be absent even in the presence of intense blood infection.

Blood Trypanosomes are present soon after infection, but are not commonly found by ordinary examination until the third week after the bite, i e towards the end of the incubation period In most cases there are relatively few; only one may be seen in several oil immersion fields in a thick film Occasionally they are numerous They remain in the blood stream for months after the onset. In the later stages, however, they become very scanty, except during exacerbations It is usually easier to find them in the gland juice

There is frequently a mild secondary anaemia in early infections In the late stages deficiencies and malnutrition complicate the blood

Serous effusions, sometimes containing parasites, have occasionally been reported in joints and in the pleural and pericardal spaces in gambiense trypanosomiasis, but are more common in rhodesiense infection.

In most cases the progress of the central nervous system lesions is continuous, but occasional cases are met in which the development is spread over a year or more, sometimes two or three years, with intermittent remissions and exacerbation of the signs and symptoms

Changes may develop in one or both eyes Conjunctivitis with excessive lachrymation is common. Corneal opacities may develop associated with interstitial keratitis and a painless iridocyclitis The retina may ultimately become oedematous The changes other than those in the retina are generally benign and resolve readily, they are not common, but must be looked for, in view of the necessity for arsenical treatment Retinal changes may lead to optic atrophy and permanent blindness

During the whole course of the nervous stage general symptoms, especially headache and glandular enlargement, may still be evident The state of the glands varies Some may be enlarged and contain trypanosomes, others may be fibrosed and inactive

Trypanosomes may sometimes be recovered from the blood or cerebrospinal fluid after centrif[illegible]

and will pass rapidly into severe malnutrition and associated deficiencies unless properly nursed and fed

Mineral and fluid deficiencies also tend to appear as the disease pro-[illegible]

Changes in the heart muscle may sometimes lead to dilatation and inadequacy This is more common in rhodesiense than gambiense infections

Males become impotent, and although there is no similar impotency in women, if they conceive during the disease abortion is common

In the uncared-for case trophic sores are common Intercurrent infection, particularly pneumococcal pneumonia and the dysenteries, are very frequent and may prove fatal Death occurs also from acute flare-up of the infection, with overwhelming trypanosome septicaemia, from cardiac or vascular failure, or from malnutrition and deficiencies

MILD AND APPARENTLY MILD CASES

The classical case is seen in local inhabitants mainly during epidemics, or in non-immune individuals such as Europeans The full picture is uncommon in the indigenous population of endemic areas, where the disease appears most frequently in a clinically mild form

worse Changes in character and personality also become prominent. Neurological signs commonly develop late.

The general condition of the patient deteriorates He becomes increasingly asthenic and easily fatigued. Unless under supervision he becomes progressively emaciated and develops signs of malnutrition and food deficiencies of one kind or another. He complains when awake of severe and persistent headache. Apathy increases; he loses interest in his surroundings, is unable to concentrate on even minor matters and has to be roused for feeding. Intellectual degeneration may be advanced A worsening confusional state is common Somnolence increases during the day, but there may be insomnia and restlessness at night Eventually the patient may pass into the inert so-called 'sleeper' stage and finally becomes comatose.

The face becomes puffy, especially around the eyelids, producing an effect of dull surly indifference, 'the swollen, stupid, rather sad look'. This facial puffiness may persist throughout the disease and be in striking contrast to the thin emaciated body.

As time goes on sensory and motor disturbances appear. These vary considerably in degree from patient to patient, one aspect often being especially pronounced in a given individual.

The sensory changes commonly affect the joints Pressure on deep tissues, for example in the palm of the hands or over the ulnar nerve, is followed by severe pain a short time after the pressure has been relieved (Kerandel's sign). Muscular cramps and neuralgic pains in the long bones and joints are common. The patient complains of tingling sensations on the lips, the soles and the palms; sometimes there may be [illegible] There may be loss of spatial sensation.

[illegible] c, emotional and depressed.

[illegible] enerates and his character disintegrates As the *meningo-encephalitis spreads neurological* changes become increasingly obvious. There may be incoordination of movements, convulsions, meningismus, hemi- or paraplegia, delirium, mania, epileptiform convulsions, coma and in the final stages incontinence of urine and faeces.

[illegible] twitch- [illegible] Tremor [illegible], which [illegible] paresis [illegible] as of [illegible] ma-tion which may be intensified by local eye changes

Incoordination and emaciation of the skeletal muscles commonly leads to a slow unsteady swaying shuffling gait. Knee jerks are usually lost late.

In individual cases the diagnosis should rest on the discovery of the parasites but in mass examination of large groups of population in endemic areas a tentative diagnosis can often be made from the clinical history, the presence of enlarged glands, and the general central nervous system picture In doubtful cases the effect on the erythrocyte sedimentation rate of a single dose of antrypol or pentamidine is often a useful lead (see below) If the diagnosis in an individual case is strongly presumed and the blood and gland juice do not reveal trypanosomes, examination of the spinal fluid is advisable In an endemic area a raised cell count and protein concentration are sometimes

[illegible]

a drop of blood on a slide with a coverslip The trypanosomes move actively about causing commotion among the red cells, and are easily visible under the high power of the microscope For final identification dried thick or thin blood films should be stained and examined by the same methods as for malaria parasites

If the parasites cannot be detected by the wet drop or thick film about 5 cc of blood may be withdrawn, citrated and centrifuged at 1000 r p m for 10 mins The supernatant fluid is removed and recentrifuged at the same speed for the same time The supernatant from this fluid is centrifuged at 2500 r.p m for a further 10 mins and the deposit is finally examined as a wet film or dried smear

Lymph gland juice Trypanosomes can usually be found in material aspirated from the glands while they are soft, they cannot be recovered from fibrosed glands The gland is lifted between the finger and thumb and pressed up against the skin A medium-sized thoroughly dry hypodermic needle is inserted into the gland substance and the gland is massaged gently. A syringe is attached to the needle and suction applied The juice in the needle is ejected on to slides, and examined either as wet or stained preparations, as for blood In *T rhodesiense* infections it may be difficult to find parasites in the glands, they should be sought in the blood

Cerebrospinal fluid The fluid is examined for the presence of trypanosomes, cells (mostly lymphocytes) and excess protein Trypanosomes are looked for in the centrifuged deposit by the wet film technique The number of cells present is calculated by the usual method, the protein is estimated by various flocculation methods

Other diagnostic points Certain other tests may help the diagnosis The erythrocyte sedimentation rate over 10 minutes is calculated and the patient is given a single dose of antrypol (0 5 to 1 0 gm) or pentamidine (150 to 200 mgm) One month later the ESR is again measured If there

which exhibits few symptoms. These forms may be truly mild or slowly progressive. The usual picture is one of mild general symptoms, including fever, and glandular enlargement, particularly obvious in the neck. There may be some wasting and at a later stage muscular tremors and [illegible]

It is impossible to tell, except by serial surveys, whether the condition is, in fact, mild or not.

In some areas the cases undergo spontaneous cure; elsewhere many of them prove fatal There is some disagreement over the cause of death in these apparently mild cases In some the full development of nervous system involvement may occur In others there is sudden exacerbation of the infection and death in septicaemia Others probably die from intercurrent infection

[illegible] develop classical sleeping sickness.

It is presumed that the milder cases seen in indigenous populations in endemic regions are the result of the development of some form of resistance to the organism acquired by previous infection Variations in the virulence of the trypanosomes may also be a factor in modifying the clinical picture

PROGNOSIS

The prognosis in untreated, well-developed severe cases is bad, especially if there is a high protein content in the cerebrospinal fluid Early cases respond well to treatment and usually recover.

The clinical assessment of an apparently mild case will depend upon some knowledge of the virulence of the local strain of trypanosomes

DIAGNOSIS

The certain diagnosis of trypanosomiasis depends on the discovery of the parasite. Search for the organism may be made in the blood, glandular juice and cerebrospinal fluid Fluid from the bite tumour taken within two days of infection usually contains parasites

in the glands of the posterior triangle of the neck Trypanosomes [illegible]

The pulse is fast from the onset and remains so even in remissions, cardiac dilatation and incompetence are common The central nervous system is involved early, sometimes within four to five weeks of the onset, but the meningo-encephalitic processes are seldom as advanced at death as those of gambiense trypanosomiasis, possibly because of the shorter duration of the disease Mental symptoms, especially progressive delusional states, are usual

Diagnosis is made as in gambiense infection

In endemic areas an increase in cells and protein in the spinal fluid should be regarded as positive evidence of trypanosomiasis until proved otherwise

PROGNOSIS

In the first few weeks after the onset the prognosis with treatment is good It gets worse the longer treatment is delayed If the disease is diagnosed late, treatment will probably fail

The untreated case usually dies within nine months or a year from the onset In some areas mild forms of the disease occur in the native population and spontaneous recovery takes place

TREATMENT OF TRYPANOSOMIASIS

Treatment is general and specific The general treatment consists of proper nursing, prevention of bed sores, adequate feeding, restoration of deficiencies in the diet, treatment of cardiovascular collapse and dehydration and so forth

CHEMOTHERAPY

The aim of chemotherapeutic treatment in both gambiense and rhodesiense infections is (i) to attempt to clear the blood of trypanosomes as quickly as possible, not only to benefit the patient but also to reduce the possibility of transmission, and (ii) to treat the meningo-encephalitis

Antrypol or pentamidine are used for clearing the blood infection, tryparsamide and Mel B for dealing with the meningo-encephalitis

AVAILABLE DRUGS

1 ANTRYPOL (suramin, Bayer 205, germanin)

is usually positive early. There may be considerable reduction in total serum protein, mainly in the albumin fraction.

Guinea pigs or rats may be inoculated intraperitoneally with 0 5 ml of blood or the final sediment from blood centrifuged as described above. Trypanosomes appear in the blood of these animals after some weeks Initial infection of animals is easier with *T. rhodesiense* than with *T gambiense.*

Mass diagnosis: Examination of large population groups for evidence of trypanosomiasis should start with a census. This is followed by systematic examination of gland juice or blood or both, for trypanosomes It is usually more economic to concentrate on examination of gland juice. In certain areas it may be necessary to examine the blood, particularly where glandular involvement is not very obvious Lumbar puncture in mass surveys should be made only in the exceptional case, and should not be carried out until the blood has been sterilized by either antrypol or pentamidine.

RHODESIENSE TRYPANOSOMIASIS

Rhodesiense trypanosomiasis is usually a rapidly developing fatal disease. The organism is largely resistant to arsenicals and treatment is effective only in the early stages

This form of trypanosomiasis follows the same general course as gambiense infection. There are certain points, however, which require special notice

The distribution of rhodesiense trypanosomiasis corresponds in East Africa to the distribution of its main vector, *Glossina morsitans* The disease is found in Rhodesia, particularly north-east Rhodesia, Tanganyika, Mozambique, Nyasaland and in certain areas of north Uganda.

ment may be severe. The latter arises from oedematous and cellular infiltration of the connective tissue of the cardiac muscle, often associated with the presence of trypanosomes, which ultimately leads to fibrotic replacement of the muscle, and corresponding loss of efficiency

In rhodesiense infection the local reaction at the bite is often severe The incubation period may be shorter than in gambiense infections The disease may start with rigor and severe fever. The lymph glands are commonly little involved although there may be some enlargement

in the glands of the posterior triangle of the neck Trypanosomes

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AVAILABLE DRUGS

1 ANTRYPOL (suramin, Bayer 205, germanin)

An organic urea substitute which usually acts swiftly against blood-borne and gland trypanosomes It is made up in 10 per cent solution in water In the adult an initial dose of 0 2 gm minimizes the possibility of idiosyncratic reactions. The full dose for an adult is 1 0 gm at intervals of 5 to 7 days until a total of 10 gm has been administered Children may be given the equivalent dose for age and weight.

Antrypol is best given intravenously, although it can be given intramuscularly. It should not be given subcutaneously.

2 PENTAMIDINE (M AND B 800)

An organic compound of the diamidine group, which is active against

each day or every other day for up to 10 days.

The initial adult dose varies from 100 mgm to 200 mgm

Children should be given dosage equivalent to weight

3 TRYPARSAMIDE

An organic substance containing pentavalent arsenic made up in 20 to 40 per cent solution in water (never in saline) and usually given intravenously The drug may sometimes be given intramuscularly

The dose is 20 to 40 mgm per kilo body weight. The initial dose for

should be a treatment-free interval of at least a month before any further administration

Tryparsamide acts only slowly on the parasites in the circulating blood, but penetrates into the cerebrospinal spaces and acts on organisms therein.

Certain other drugs have been tried with some success in rhodesiense infections. The most promising of these is Mel B

4 MEL B (Friedheim)

Melarsen Oxide B A L and similar compounds including Mel W have recently been successfully used in severe gambiense sleeping sickness and in rhodesiense trypanosomiasis. Mel B is given intravenously. Mel W has the advantage of being water-soluble and is given intramuscularly or subcutaneously

DETAILS OF TREATMENT

(1) *The average case*

The early stages of both infections may be successfully treated with either antrypol or pentamidine

It is better, however, to treat all cases as though the cerebrospinal spaces are involved

Such treatment demands the combination of tryparsamide with either antrypol or pentamidine

Successful combinations of drugs are given below The dosages are those given in mass campaigns In individual cases the tryparsamide may be continued for a further 4 doses

Except in the very earliest cases, rhodesiense infections should be treated with pentamidine (or antrypol) and Mel B

(a) *Combined Treatment*

Day	*Drug and Dose*
1	Antrypol 0 2 gm
6	Antrypol 1 0 gm
11	Antrypol 1 0 gm
16	Antrypol 1 0 gm
(Total of 3 2 gm Antrypol)	
21	Tryparsamide 1 0 gm
26	Tryparsamide 2 0 gm
31	Tryparsamide 2 0 gm
36	Tryparsamide 2 0 gm
41	Tryparsamide 2 0 gm
(Total of 9 0 gm Tryparsamide)	

Pentamidine may be substituted for antrypol in the following doses
First dose 100 mgm Follow by 150-200 mgm daily for 6 days
After a 5-7 day interval commence tryparsamide treatment as above.

In dispensaries where large numbers of cases are treated, the drugs are often made up in solutions so that 10 ml contains the full adult dose. Tables of dosage corresponding to the weight of the patient are then easily prepared For example

Weight of patient	*Dose*
100 lb or more	10 ml
80 lb	8 ml
etc	
19-15 lb	1 5 ml
14 lb or less	1 0 ml

(Solutions Antrypol 1 gm in 10 ml Tryparsamide 2 gm in 10 ml)

(b) *Simultaneous Treatment*

Antrypol 0.5 gm and tryparsamide 1.5 gm are given on the same day. Injections are given on six occasions at 5 to 7 day intervals.

(Total of antrypol 3.0 gm and tryparsamide 9.0 gm.)

The schedule of treatment (b) above has the advantage of being quicker in administration, but it is more toxic than schedule (a) which is more commonly used.

If a course of treatment is unsuccessful, it may be repeated after not less than a month from the last dose of tryparsamide.

(ii) *Rhodesiense infections and severe gambiense sleeping sickness:*

Mel B should be given in very advanced cases of gambiense sleeping sickness and in cases of rhodesiense trypanosomiasis in which the cerebrospinal system has become involved.

It is always given with the standard course of either antrypol or pentamidine in order to remove the trypanosomes from the blood.

A standard method of administration is as follows.

The dosage is divided into 'dosage units' representing 3.6 mgm per kilo. A total of 5 to 7 'dosage units' is given over a period of one month in four groups of doses with rest periods in between.

Dosage of Mel B, giving a total of 7 'dosage units'

Days of treatment	1	3	5	10	11	12	19	20	21	28	29	30
Fraction of a 'dosage unit' given on each day (in tenths of a 'unit')	1	2	3	5	5	5	6	7	8	8	10	10

RESPONSE TO TREATMENT

Treatment is usually successful in relieving signs and symptoms in gambiense infections and leads to recovery except in very late stages. The trypanosomes often disappear from the blood stream within a few days. They are slower to go from the spinal fluid. Rhodesiense infections do not respond well to treatment once the cerebrospinal system has become involved. Advanced gambiense sleeping sickness and rhodesiense infections may respond well to Mel B.

The progress of an individual case may be checked by periodic examination of the spinal fluid. The cellular count usually falls faster than the protein concentration.

TOXICITY

Arsenical compounds may be very poisonous. There may be early gastrointestinal disturbances with diarrhoea and vomiting. With

tryparsamide dermatitis is rare The most serious effect is on the optic nerve, which is indicated by gradual or sudden dimness of vision, with central or peripheral narrowing of the fields of vision, scotomata and ultimately complete blindness The ophthalmoscope will show no changes in the early stages

The toxic visual effects are often preceded by photophobia, increasing lachrymation, ocular pain, and dimness of vision The risk of using arsenicals is increased in cases in which the trypanosomes have already initiated eye changes

Antrypol may affect the renal epithelium Severe renal damage is only occasionally seen The urine should be examined in all cases before and during treatment If there is any sign of renal disease or if albumin with casts and blood cells appear during treatment, antrypol should be withheld and pentamidine substituted

ARSENIC RESISTANCE

Resistance to arsenicals including tryparsamide may be quickly acquired by both *T gambiense* and *T rhodesiense* infections This resistance persists indefinitely and is not lost by cyclical transmission in Glossina flies It constitutes a major problem in the mass treatment of trypanosomiasis Mel B is usually active in resistant cases

PROPHYLAXIS

Both antrypol and pentamidine are excreted slowly from the body The concentration of the drugs in the tissues will thus remain sufficiently high to prevent infection for a considerable period after injection Injection of 1 gm antrypol in an adult protects against infection for 6 to 12 weeks A single dose of 200 to 250 mgm pentamidine protects for 3 to 6 months

AMERICAN TRYPANOSOMIASIS

DEFINITION

Chagas disease An acute, subacute or chronic condition caused by the pleomorphic *Trypanosoma cruzi*, transmitted by certain large bugs The acute disease occurs mainly in children It is characterized by

GEOGRAPHICAL DISTRIBUTION

The disease is scattered irregularly in North and South America, in a wide area stretching from Mexico in the north to the Argentine in the south The distribution of the vectors and animal reservoirs is very much more extensive than that of the human disease, which is limited to certain areas within this wide belt. It is found in various parts of Venezuela, Brazil, west Argentine, Uruguay, northern Chile, Peru and Ecuador It has been reported in Guatemala, Panama and Mexico

The disease does not occur outside America, although the vectors and reservoir animals are common to many other parts of the world

AETIOLOGY

CAUSATIVE ORGANISM

The disease is caused by *Trypanosoma cruzi* which closely resembles the trypanosomes of African trypanosomiasis In the blood the organism is found as slender or stumpy trypanosomes 15-20 µ in length, with the usual undulating membrane and anteriorly placed flagellum. The nucleus is central and the large oval kinetoplast posterior *T cruzi* propagates in the tissue cells, not in the blood

THE VECTOR

The disease is transmitted by large biting reduviid bugs belonging to the family *Triatomidae*, particularly by *Panstrongylus megistus* and *Triatoma infestans* The larva, nymph and adult bugs all transmit the infection; the latter is the most important.

The bugs are found under dirty unhygienic conditions associated with either humans or animals. They are active only in darkness, so that transmission usually occurs at night. It is possible to convey infection artificially through other insects, including the bed bug, but it is doubtful whether any of these is important in natural transmission

LIFE CYCLE IN THE VECTOR

tive to man Once infected, the bug remains infective for life.

RESERVOIRS OF INFECTION

of animals transmitted accidentally to man In other areas, especially in villages, man is the important reservoir.

The organism has been identified in animals in areas as far north as southern California, Arizona and Texas, in none of which has the human disease been reported

TRANSMISSION

Although the trypanosome present in the blood of human cases or of reservoir animals is infective to man, transmission in nature occurs

the latter occurs most frequently in the lips or the conjunctiva The bite of the bug is important only in so far as it causes a break in the skin surface and thus facilitates the entry of the parasite

The high incidence of transmission in children is probably the result of the greater ease with which the parasites can penetrate the delicate skin, and the greater risk of exposure to biting

Infection is said to occur occasionally across the placenta, or by way of infected mother's milk Metacyclic forms survive for days in dead bugs and may cause infection if the latter are accidentally eaten

The disease occurs mostly amongst the lower economic groups living in poor squalid conditions in small villages The appearance of the disease in a given community is highly erratic Children are most commonly affected The sexes are affected about equally

There is no clear correlation between either the incidence of the infection in accessible reservoir animals or in bugs Even when the latter show a very high rate of infection in a particular village, for instance, the known case incidence may be very low

There is no seasonal incidence and no explanation for the very irregular distribution in relation to reservoirs and vectors It is possible that more careful investigation will reveal a much wider distribution than at present suspected

PATHOLOGY

The tissues into which the infective metacyclic forms penetrate react vigorously In the course of a few hours local oedema, with some

within a few days and gives rise to the early septicaemic signs of the disease The spleen and liver eventually both enlarge

The more severe lesions of the various organs in the later stage of the disease arise primarily as a result of the further leishmanioid development of the parasite within the tissue cells.

The trypanosomes immediately *enter local reticuloendothelial cells* at the site of inoculation Within the cells they undergo a leishmanioid stage of development and later return to the tissue spaces and blood as trypanosomes, re-entering other tissue cells and repeating the cycle In *this way the cells of many tissues become invaded and destroyed* This process is particularly notable in the macrophages of the spleen, the

infection

In the acute progressive form of the disease, which constitutes about 20 per cent of the infections in infants, massive myocardial involvement

during the leishmanioid cycle Where there has been extensive involvement of the heart myocardial damage may appear in later life, as a result of the large areas of muscle replaced by scar tissue

Leishmanioid organisms may appear in the cells in other organs including the thyroid and supra-renal Goitrous changes in the thyroid gland are common in some districts, these are not direct effects of the disease but are due to local mineral deficiencies

Meningo-encephalitis may occasionally develop The meninges and brain tissue may be oedematous, congested and infiltrated, there are scattered neuroglial and round cell infiltrations, especially about vessels Small granulomata may develop around trypanosomes or leishmanioid forms lying in the brain substance in the region of the small vessels

Changes in the spinal fluid similar to those in the latter may be present in cases in which the central nervous involvement is considerable

T cruzi may remain in the blood for long periods In the ordinary course of events during the acute attack trypanosomes are present in the largest numbers during the early stages In mild cases or in the 'chronic' stage they may be difficult to demonstrate in the blood, except by indirect biological methods such as xenodiagnosis

It is believed that *T cruzi* trypanosomes as such are in some way responsible for the fever Trypanosomes are found in considerable numbers in the blood during the acute stages of the disease The occa-

invaded tissue cells

Unfortunately, the degree of parasitaemia in a given case is no real

measure of the damage progressing in the tissue cells invaded by the leishmanioid forms

CLINICAL PICTURE

American trypanosomiasis may appear in acute or in subacute or chronic forms

The incubation period is usually 1 to 3 weeks

THE ACUTE DISEASE

The acute disease is commonest and most severe between the ages of 1 and 5 years It may occur occasionally in adolescents or adults, usually in milder form

The outstanding clinical pattern after onset is one of severe and intensifying myocardial damage In heavy infections in which the damage to heart muscle is extreme, a fatal issue is certain during the first acute attack In less severe cases in which the myocardium is less damaged, recovery from the initial febrile illness occurs after some months and the condition passes into a more chronic state in which the final picture is decided by the ultimate pathological disturbance of the cardiac muscle Such cases may survive to adult life with irregular intermittent febrile attacks A proportion of infections may not produce an initial severe febrile episode and may not be detected for years. These cases are usually diagnosed during routine examination by the discovery of some degree of myocardial damage

The onset of the febrile attack is commonly preceded by local reactions to the original inoculation of the parasite In a single infection these reactions, when on the face, are often unilateral (as described below) but infection may occur at frequent intervals especially under the prevailing social circumstances in which infants become involved, so that bilateral facial reactions are common.

The Chagoma reaction The first sign of infection is usually the appearance within a few hours of a swelling at the site of entry of the metacyclic infective trypanosomes This rapidly becomes a hard elastic

It may occur also on the abdomen and limbs, especially the thighs Occasionally metastatic swellings develop, especially in older children, for instance, they may appear on the face or arms following actual infection in the legs If untreated the swelling may become very large and intensely painful

The chagoma reaches its full size in a few days and may last as long as two or three months It may have faded by the time the general signs of infection have developed



FIG 54 Chagas disease in child of two Note unilateral facial and palpebral oedema [Courtesy of *British Encyclopaedia of Medical Practice*, Butterworth & Co (Publishers) Ltd, 19-23 Ludgate Hill, London, E C 4 Photograph by Dr Mazza]

The skin over the plaque and at its edges becomes hard and may desquamate. Suppuration does not occur unless there is secondary infection The lesion usually disappears completely but in some cases especially on the abdominal wall or thigh, there may be slight scarring or some depigmentation In hairy parts healing may be followed by alopecia

The glands draining the point of infection are usually palpable by the third day and may become considerably enlarged and remain so for weeks. The glands are firm, mildly tender and discrete. The skin over them is often erythematous and oedematous. In a group of glands there is often one which is much more enlarged than the others

In a few cases there may be no local reaction and the first sign of infection may be the glandular enlargement

When the face is involved, the glands most commonly affected are the pre- and post-auricular, and the submaxillary.

Local oedema The appearance of localized areas of oedema is very common in the first few days of the disease The oedema develops suddenly It may persist for months or subside in a few days, sometimes before any general signs develop

Unilateral involvement of the eyelids is the commonest finding (*Romana's sign*) Both lids are swollen with a hard elastic non-pitting oedema The oedema may remain confined to this area for some time, but more commonly spreads down into the cheek and sometimes to the neck. The eyelids of the other side may become involved; sometimes oedema may develop bilaterally

The skin over the oedematous areas is often erythematous and blotchy, giving the appearance of bruising

Oedema of the eyelids is accompanied by swelling and injection of the local conjunctiva The lachrymal glands are frequently affected,

and the eyelashes may be glued together with coagulated serous exudate. In the absence of secondary infection the condition is not purulent

From time to time during the early stages of the disease local areas of hard oedema may develop in any part of the body, particularly in the scrotum, the legs, the lower abdominal wall and the pubis The appearance of oedema in the limbs is sometimes accompanied by a spread of the oedema of the face and even by generalized anasarca, in young infants

GENERAL REACTIONS

The general signs and symptoms commonly appear 4 to 14 days after infection and the appearance of local signs The patient is restless and sleepless He suffers from malaise, increasing exhaustion, chills, and bone and muscle pains There is often epistaxis Convulsions are common in young children; they are usually infrequent and severe and may be fatal

Trypanosome forms of *T cruzi* appear in the blood in about 10 days, and may be present throughout the acute stage

With the invasion of the blood stream the general reaction develops The local lesions described above persist for varying periods, often for months

Fever The general symptoms usually start with a moderate remittent fever, which may continue for several weeks Sometimes in infants, the initial fever is very high and continuous In other cases it may be mild and of short duration During the fever the pulse rate is fast (110 to 150 beats per minute) and there may be soft mitral bruits In severe cases in which there is intense myocardial damage acute cardiac failure develops often within a few days of the onset of the fever The respiration rate is fast and there is frequently some minor bronchial involvement with cough, which may tend to mask the condition The spleen becomes palpable in the first few weeks, but is seldom prominent The liver enlarges early and may be palpable for several finger breadths below the costal margin

A moderate degree of general glandular enlargement is present in most cases within a week of the appearance of the local signs of infection The glands are only slightly enlarged, not very tender, and in the early stages contain trypanosomes.

There are no characteristic changes in the erythrocytes The white cell count is raised In infants the increase is seen mainly in large mononuclears, in older children, in lymphocytes, which may represent as much as 70 per cent of total white cells

In a small proportion of cases there may be fleeting morbilliform, papular or urticarial rashes Later there is often depigmentation or

hyperpigmentation of the skin over the site of the healed chagoma or in areas which have been oedematous

Cardiovascular system A very fast pulse is an indication of serious myocardial lesions resulting from repeated invasion of the muscle cells and the repetition within them of the leishmanioid cycle of the parasite. In the active stage, especially during the first week in infants, sudden dilatation of the chambers of the heart may lead to failure. The muscle lesions may also lead to various changes in cardiac rhythm, including fibrillation and heart block with corresponding changes in the electrocardiogram; the Stokes-Adams syndrome has been reported.

All cases in which cardiac involvement is extensive from the beginning will die within weeks or months In less severe infections the cardiac involvement may subside spontaneously or pass on to the later fibrotic stages which are seen commonly in older children or adults

Occasionally cardiac symptoms may appear without any other indication, local or general, of the infection. Cases in which this occurs are usually seen later in life

Involvement of the central nervous system is commoner in infants than in older children Suckling infants may die in a few days from the meningo-encephalitis, before the cardiac changes have developed The symptoms are mainly cortical Convulsions are severe and death occurs during them or in deep coma Meningismus may be present.

The majority of cases show a minimum of nervous involvement and pass through the acute illness without any evidence of it.

In those in which the cerebrospinal system is involved the fluid is at high pressure and contains excess lymphocytes and proteins *T cruzi* may sometimes be found in the centrifuged deposit

The duration of the acute stage is variable Severe cases may terminate fatally in a few days, especially in infants. More commonly it continues for weeks or months, the issue depending on the severity of the myocardial involvement When this is severe death results. When it is only moderate, recovery occurs and the patient passes into a subacute or chronic state, in which febrile episodes may appear at long intervals and in which fibrotic cardiac lesions become slowly established

SUBACUTE AND CHRONIC STAGE

The subacute disease is seen as a rule in older children from 5 to 10 years of age. There is commonly a history of an acute attack followed by a period of remission with or without mild fever, and sometimes with occasional exacerbations of severe symptoms There may, however, be no history of an acute attack

In the subacute stage local signs such as facial oedema, if present in the acute phase, have usually subsided If in a period of remission the

patient is listless, often mildly feverish, and has a persistently fast pulse Arrhythmias are common

The condition progresses to slow recovery but remissions occur subsequently from time to time This goes on for years The late stages are commonly associated with some permanent myocardial insufficiency

Trypanosomes are difficult to demonstrate in the blood stream even during the fever, except by biological methods

subacute disease, or with demonstrable parasites in the blood or detectable by xenodiagnosis It is not clear how far the latter diagnosis is justified, since it is possible that at this stage a state of tolerance has been achieved between host and parasites

In some endemic areas myocardial involvement is more frequent amongst adolescents and young adults than elsewhere, and there is a tendency to include in the diagnosis of trypanosomiasis even cases without a history of infection or circulating parasites

Cases present with all stages and types of myocardial involvement In severe cases sudden death may occur and is often blamed on the disease

PROGNOSIS

The prognosis is bad in infants, especially when cardiac damage is severe Early dilatation of the heart, persistent severe arrhythmia or pericardial effusion are unfavourable signs It is bad in any case in which the nervous system is obviously involved

In the subacute and chronic stages the prognosis depends entirely on the extent of myocardial involvement

Malnutrition and coincident infective conditions, especially malaria, are serious complicating factors

DIAGNOSIS

Clinical diagnosis in an endemic area is usually easy in young children Unilateral oedema of the face, especially of the eyelids, together with non-purulent conjunctivitis, the presence of a chagoma and locally involved lymph glands are all indicative of the disease Meningo-encephalitic signs in infants and young children and persistent tachycardia, arrhythmia or cardiac dilatation, especially when associated with fever or any of the local signs above are highly suggestive

Certain diagnosis needs the demonstration of trypanosomes.

LABORATORY DIAGNOSIS

Blood Wet and stained thick films should be examined as in African trypanosomiasis The trypanosomes are fragile and easily damaged For this reason it is better to examine fresh films in all cases

Trypanosomes are not usually present in large numbers except in very young children during the early acute disease In older children and adults they are present only during remissions and may be missed by direct blood examination; indirect methods may be necessary.

Identification of the species of trypanosomes is important, since *T rangeli* (which produces no clinical effects) may be present in the blood of individuals in areas in which Chagas disease is endemic.

Lymph gland juice Trypanosomes may be present in the juice of the [illegible]

Cultures should be examined after 21 days.

Cerebrospinal fluid: The deposit after centrifugation of the cerebrospinal fluid may rarely contain the trypanosome in cases in which there is evidence of meningo-encephalitis The preparation of material for examination is the same as for *T. gambiense.*

BIOLOGICAL TECHNIQUES

Xenodiagnosis: Bugs raised in the laboratory and known to be uninfected are allowed to feed on the forearm of the suspected case for 15 minutes The faeces are examined for metacyclic forms after 30-60 days Infected bugs should be killed and examined in groups at intervals up to 60 days after feeding Control groups of bugs are similarly examined for infection with *T. rangeli*

Animal inoculation Mice or puppies are readily infected by *T. cruzi.* [illegible]

period of 5 to 25 days after injection The animals are finally sacrificed and a search is made for leishmanioid tissue forms in the tissues, especially the heart These may be present in animals in which parasites were not found in the blood. The organism will survive for hours in citrated blood

Complement fixation Serum from the suspected case may be used in a complement fixation reaction (the Machado test), in which the antigen is an extract of organs, usually the liver, from an animal dead of the disease, or an extract of cultures of the trypanosome A positive result is of presumptive diagnostic value. Weak positive reactions are given by sera from cases of cutaneous leishmaniasis.

The test should always be associated with other diagnostic methods Some authors regard the complement fixation reaction as more reliable than xenodiagnosis

Biopsy of an enlarged gland, with examination of smears and histological sections stained to reveal leishmanioid parasites may be helpful in some cases, but is not usually needed

TREATMENT

Treatment is unsatisfactory Drugs successful in African trypanosomiasis are ineffective

Certain synthetic compounds have been found to have some action against the trypanosome form of the parasite, but these and all other drugs so far tried are inactive against the leishmanioid forms responsible for the major tissue damage.

The use of trypanosomicidal drugs is therefore ineffective once the leishmanioid invasion of cardiac muscle, etc , has become extensive They may be helpful if given very early in mild infections or during remissions

Some control of blood trypanosomes has been demonstrated with various drugs including Bayer 708 and 7602 Cure is not achieved

CONTROL

Improvement in hygienic conditions, especially housing, is the first essential. Bugs can be dealt with by DDT or Gammexane. Chemotherapy of known cases helps to reduce the infectivity of local bugs

XXXVIII

THE TYPHOID FEVERS

DEFINITION

ENTERIC, or typhus abdominalis, is due to infection with *Salmonella typhi* or with *Sal. paratyphi* A, B or C. The disease is characterized by an acute course of about three weeks' duration, with fever, toxaemia, abdominal symptoms, enlargement of the spleen, and a cutaneous eruption The mortality is considerable with the first mentioned of these infections

GEOGRAPHICAL DISTRIBUTION

Typhoid fever is world-wide in distribution and occurs irrespectively of climate Nevertheless, with improved water supplies and sanitation, in the better developed temperate climates its incidence has steadily decreased and it now is much more prevalent in the tropics than in the colder parts of the globe

AETIOLOGY

The causal organisms, which belong to the Salmonella group, enter man solely by the alimentary tract. The only source of infection is the infected excrement of human beings harbouring the organisms These

infection, and about 2 per cent become chronic carriers The majority

have not suffered from an attack of typhoid but in whom the infection has been a non-pathogenic intestinal one, at a later date in these cases the infection may become systemic, and the patient then suffers from

by pollution of the containers during rinsing; the resultant typhoid epidemic under such conditions is usually widespread If milk, bread or other comestibles are contaminated by a typhoid carrier during

production the epidemic is limited and is related to the distribution of the contaminated product House flies, by virtue of their habits, are important vectors of the infection and are responsible for many sporadic cases of typhoid

Typhoid is principally a disease of adolescents and young adults It occurs in children, but in them takes a less severe form, it also occurs in the middle-aged and aged, its clinical severity and the case mortality due to it increase with advancing years There is no racial immunity to the disease

The concentration of susceptible individuals under defective sanitary conditions, such as camps, favours the occurrence of severe epidemics

PATHOLOGY

The normal acid content of the stomach is one of the chief defences against this and other similarly acquired bacillary infections This physiological barrier is readily broken down by dilution with draughts of fluid, by emptiness of the stomach, and by other means, and the bacilli then pass into the small intestine

The bacilli probably enter the Peyers patches or solitary lymph follicles, where they rapidly multiply and quickly pass by the lymph vessels into the blood stream There is thus a very early bacteraemia The organisms soon reach the bile, either directly from capillaries in the gall bladder wall or indirectly by the liver capillaries into the bile canaliculi, and flourish in it A second and heavier invasion of the intestine through the infected bile takes place It is this second invasion which is responsible for the extensive lesions in the lymphoid tissue of the small intestine characteristic of the disease, and it is when they appear that the grosser clinical manifestations of the disease become evident

Typhoid is essentially a bacteraemia with generalized infection and profound toxaemia It affects the haematopoietic system, especially the lymphoid tissue of the small intestine, the abdominal lymph glands, the spleen, and the bone marrow, but any organ may be involved In lymphoid tissue the organisms cause a peculiar cellular reaction, there are very few polymorphonuclear cells in the lesions, but there is hyperplasia of the lymphoid cells with the appearance of numerous large mononuclear phagocytic cells ('typhoid cells') which probably are derived from the reticulo-endothelial system These cells commonly phagocytose lymphocytes, red cells and other cells

In the small intestine the lower part is that most involved; sometimes the caecum and uppermost part of the colon are affected; and sometimes, especially in *Salmonella paratyphi* B infections, there are lesions throughout the whole of the large intestine and in the stomach The

Peyers patches and solitary follicles at autopsy are found to be hyperaemic, swollen and raised above the surface. The infiltration and engorgement of the adjacent submucous and muscular coats render the lesions visible from the outside of the bowel when fully developed about the tenth day of the disease

In mild cases these lesions may resolve without any necrosis In the classical case superficial necrosis occurs early in the second week of the disease; this in part may be due to toxins, but chiefly it is caused by the blockage of small vessels by large numbers of the 'typhoid cells'. The necrotic mucosa forms a slough which separates during the third week, leaving an ulcer The typhoid ulcers are rounded or irregularly oval, with their long axes in that of the bowel; they are located on the antimesenteric part of the bowel. Many of them are quite shallow; but often the submucosa is penetrated and the floor lies on the muscular or even the serous coat of the intestine.

Separation of the sloughs may lead to gross haemorrhage from damaged vessels, or to perforation of the gut wall. These two complications, haemorrhage and perforation, account for many deaths There is no exact relationship between the severity of the disease and the severity of the ulceration, the former is proportional to the toxaemia, but haemorrhage or perforation may occur during clinically mild attacks of typhoid

The ulcers heal by granulation during the fourth week, with little scarring; they *eventually are covered with simple epithelium free from* glands

The mesenteric glands are swollen and soft, and often are haemorrhagic, the lymph sinuses are distended with the characteristic large phagocytic typhoid cells. One or more abdominal lymph glands may necrose and rupture causing peritonitis. The spleen is moderately swollen and hyperaemic. In it there are small areas of necrosis with collections of typhoid cells

There are similar lesions in the liver, which shows the cloudy [illegible]

[illegible]

attack of enteric the infection may persist in the gall bladder and bacilli continue to appear irregularly in the stools. The patient is now an intestinal carrier

[illegible]

occasionally persists after recovery of the patient from the disease. He becomes a urinary carrier of the infection

The heart muscle is soft and swollen due to a toxic myocarditis, pericarditis may occur especially in children, but typhoid endocarditis is rare Thrombophlebitis, especially of the left femoral and saphenous veins, is not uncommon, thrombosis of the cerebral sinuses sometimes occurs Periostitis, abscess, or necrosis of bones may complicate the acute disease, but more often they appear months or even years after apparent complete recovery from it The tibia, sternum, ribs and vertebrae are those bones most affected, and typhoid bacilli can be recovered from the lesions Bronchitis and pneumonic consolidation are common Meningitis occurs very occasionally, and is then usually associated with a middle ear infection

Within the abdomen the typhoid bacilli cause non-pyogenic lesions, but extra-abdominally they may produce suppurative lesions In the early stages of the fever there is a blood leucopenia, with an increase in the lymphocytes and mononuclear cells In the later stages, when there is ulceration of the bowel with secondary bacillary infection, there is a leucocytosis, the increase in lymphoid cells is then obscured by a marked increase in the polymorphonuclear cells The latter state of affairs is also evident when there are suppurative extra-abdominal lesions

CLINICAL PICTURE

The incubation period ranges from 7 to 21 days, it is usually 10 to 12 days The onset commonly is insidious with anorexia, lassitude, a frontal headache and muscular pains, a furred tongue and often some gastro-intestinal upset There is a slight evening fever which may escape notice

The first week Shivering attacks may occur as the temperature, with remissions, mounts daily to 103° or 104° F by the end of the week The pulse-rate is 80 to 100, and the pulse remains soft and is dicrotic There commonly is epistaxis, and the earlier symptoms increase as the patient becomes prostrated There is an increase in the respiration rate with signs of catarrhal bronchitis The abdomen becomes distended and uncomfortable, there may be either diarrhoea or constipation initially, but by the end of the week there is usually diarrhoea The face becomes drawn and pallid, there is a circumscribed flush on the cheeks, the tongue is furred but red at the tip and edges, the throat is dry and inflamed

A rash appears on the 6th or 7th day It is restricted to the abdomen and flanks as a rule, and is sparse It consists of successive scanty crops of small rose-coloured spots, each 2 to 4 mm in diameter, which

fade on pressure Each spot lasts for three or four days and then disappears completely The crops may continue to appear over ten to eighteen days In grave cases diffuse purpuric skin eruptions may appear

The second week The temperature is maintained at a high level, with slight morning remissions. The toxaemia becomes more marked; there often is a low muttering delirium Deafness is usual The tongue becomes dry, glazed and red; sordes collect on the teeth. The pulse rate quickens and the blood pressure falls. There commonly is basal congestion of the lungs The spleen becomes palpable. There is an increase in the abdominal distension and discomfort as the intestinal lesions further develop, usually there is diarrhoea, and the stools become dark due to some escape of blood from the lesions

The third week In favourable cases the symptoms begin to lessen, and the remissive temperature slowly declines. But the grave and common complications, haemorrhage and perforation, are prone to occur as the sloughs separate from the ulcers In very severe cases the condition of

at the bedclothes Tympanites and meteorism may occur; extreme abdominal distension may be followed by pain and collapse, a rapid pulse and local or general peritonitis indicate perforation. Cold sweats, restlessness, sighing respirations, and collapse of the palpable pulse indicate haemorrhage Toxic myocardial degeneration is a common cause of death Incontinence of faeces and of urine is usual during this state.

The fourth week In favourable cases convalescence is entered upon Sometimes lobar pneumonia or thrombophlebitis, especially of the left femoral vein, may appear in its early stages

Relapses In those who develop only a feeble immunity, commonly as a result of a mild attack, a relapse occurs some ten days after the end of the primary attack. The relapse resembles in a mild form the primary attack and usually is of shorter duration Relapse occurs in about 10 per cent of cases As many as four or five relapses have been recorded in exceptional cases

recovery
ive rise
yphoid
bacilli can be recovered by culture of the discharge

A persisting infection of the gall bladder, or of the kidneys, results in the carrier state *in a proportion of cases*

DIAGNOSIS

The definitive diagnosis rests on recovery and identification of the causal organisms Blood culture during the first 14 days of the disease usually yields a growth of the organism Some 6 ml of blood is withdrawn aseptically from a vein, half of this is sown into bile salt broth to recover the typhoid bacilli, and the remainder into glucose broth for other organisms Where suitable media are not immediately available the blood may be allowed to coagulate, the clot is then subsequently cultured

After about the tenth day of the disease the Widal test becomes positive, and it rises in titre until the disease ends Previous prophylactic inoculation with T A B vaccine causes an increase in the agglutinins for the typhoid organisms, repetition of the Widal test at two-day intervals with evidence of a progressively rising titre of agglutinins is necessary for a positive diagnosis of an active infection

Culture of the faeces during the second and third weeks, if repeated, usually will yield organisms, culture of the urine repeated on several occasions does so usually during the third and fourth weeks

The blood picture is helpful in differential diagnosis as there is a polymorphonuclear leucopenia with a relative lymphocytosis during the first ten days of an attack of typhoid Thereafter secondary bacterial infection of the intestinal lesions usually causes a polymorphonuclear leucocytosis Perforation is followed by a rapidly rising polymorphonuclear leucocytosis and this should be watched for

TREATMENT

The diet should be nourishing and readily assimilable; it should be given in small quantities at frequent intervals, it should be as liberal as possible, and it should be free from all indigestible and fermentable matter The fluid intake must be adequate to compensate for that lost from the bowel and as a result of the fever The temperature when it mounts over 102° F should be reduced by sponging The strictest precautions must be taken to disinfect or destroy all linen soiled with infected excreta, and the latter must be promptly disinfected, flies being denied access to them

Chloramphenicol (chloromycetin), one of the antibiotics has been demonstrated both *in vitro* and *in vivo* to exert a powerful bacteriostatic action on these organisms, but it is not bactericidal to them It controls the multiplication of the organisms and the progress of the infection until the natural defensive mechanism overcomes them If given in inadequate amount, or for a period insufficient for the body to develop an immunity to the organisms, relapse follows its use Chloramphenicol

is ineffective in sterilizing intestinal or urinary carriers of their infections

[illegible]

during the second or third week will arrest the progress of the infection and produce symptomatic relief, but the dangers of haemorrhage and perforation are not eliminated if gross lesions have developed in the intestine when the specific treatment is begun

The successful treatment of carriers is less simple. Extirpation of the gall bladder in most cases will free the intestinal carrier of his infection There is no satisfactory means of clearing the renal infection in an old-standing urinary carrier.

Prophylactic inoculation with T.A.B vaccine of those entering [illegible]

but it may be treated with alcohol. The latter procedure is said to be less destructive of the Vi antigen than treatment by heat; the reaction following injection of the alcoholized vaccine is said to be less severe than that of the heat-treated Although alcoholized vaccine was at first claimed to be a more effective immunizing agent, it has not sustained this reputation on extended trial T A B inoculations should be repeated yearly for a number of years Though vaccination reduces the incidence of infection it does not provide absolute immunity; those who acquire the disease in spite of inoculation suffer rather less severely than the completely unprotected

XXXIX

THE TYPHUS FEVERS

INTRODUCTION

THE typhus fevers are diseases of man due to infection with one or other of a number of species of rickettsial organisms Most of these organisms normally affect rodents, and the infection of man by them is incidental and sporadic Usually they are conveyed from one host to another by arthropods, certain lice, fleas, ticks and mites being those which specifically transmit various types of typhus fevers to man The diseases in man are characterized by a short incubation period and an acute course of about two weeks' duration, this is associated with sustained fever, severe toxaemia, an exanthem which

borne typhus and mite-borne typhus, are more localized and the latter is confined to the Far East

TYPES

Louse-borne. Epidemics of louse-borne typhus fever have been recognized since the sixteenth century, and their particular association with wars, famine and similar disasters has long been appreciated. Though the role of the human body-louse in disseminating the infection from man to man has long been suspected, it was not until 1909 that it was proved *Pediculus humanus* feeds exclusively on human blood, on engorging a blood meal from a patient suffering from epidemic typhus it becomes infected with *Rickettsia prowazeki*, the causative organism The organisms enter the cells lining the gut of the louse and multiply freely in them, after some days rickettsias are passed in the faeces of the infected louse Lice leave a febrile skin or a cold one, and the migration of infected lice from the bodies of the sick or dead to other individuals is readily effected under conditions of squalor and overcrowding Lice transmit the rickettsial infection by contaminating skin abrasions with their infected faeces, or by being crushed and ruptured with the inunction of their infected guts and gut contents into the skin by scratching They do not infect by bite The lives of lice infected with *R prowazeki*

are shortened by the infection, infected female lice do not transmit the infection through the eggs to their offspring.

In addition to infection by this the normal way, through personal infestation with infected lice, individuals may acquire the disease without themselves becoming lousy by inhalation of dried infective louse faeces It is thus that doctors, nurses and others, in spite of adequate protection against louse infestation by special clothing and insecticides, may sporadically acquire the disease when in contact with it professionally Epidemic louse-borne typhus is the only disease of the group which is confined to man, there is no other recognized animal reservoir *of the infection; the human body-louse is the only arthropod vector of* the infection, and in its absence the disease does not occur.

Since the recognition of the specific aetiology of epidemic louse-borne typhus, there has been much progress in knowledge of a number of allied diseases of similar causation All of these are due to rickettsial organisms, but with the possible exception of that causing Fièvre Boutonneuse these organisms normally are enzootic in rodents and small mammals, and man is only an accidental and therefore sporadic host of them The infections are not normally transmissible by the human louse or human flea, they do not spread from man to man and so they do not occur in epidemic form and at most do so endemically.

Flea-borne During the last half century sporadic cases of typhus have been recognized in the apparent complete absence of the classical epidemic louse-borne disease These cases were not followed by spread of the infection to contacts It has now been established that rats and mice are subject to rickettsial infection with an organism generally referred to as *R mooseri* This infection is conveyed from one animal to another by the rat louse *Polyplax spinulosus* or the rat flea *Xenopsylla cheopis*, both of which become infected by blood meals on infected animals and subsequently pass the organisms in their faeces Man, if attacked by *X cheopis in search of a blood meal, becomes infected with R mooseri* through the faeces of the infected fleas, and he then develops an attack of 'murine' typhus The disease does not spread from man to man as his own ectoparasites, the louse *P humanus* and the flea *Pulex irritans*, are not effective vectors of *R. mooseri*

It has been suggested that murine typhus infections in man may under certain circumstances become adapted to free transmission by the human louse, and that this is the origin of epidemic louse-borne typhus This theory has not been sustained experimentally, but it would account for the appearance of epidemic louse-borne typhus in communities in the absence of its introduction from a recognized extraneous source of infection Furthermore it receives support from the fact that the epidemic louse-borne and the murine flea-borne forms of typhus clinically are indistinguishable and immunologically are very

of fevers occur in men traversing or working in sharply defined riverine areas of bush country In Japan for many years it has been known that the disease there called tsutsugamushi, or Japanese river fever, is conveyed to man by mites These mites derive their infections in the preceding generation from small rodents which are the normal hosts of the causative organism, *Rickettsia orientalis* The mites, which belong to several species, take but a single meal from warm blooded animals

mite becoming infected on the occasion of its only mammalian meal can pass on the infection to its offspring, the latter then transmit the infection to a new host by their bites on the occasion of their single tissue meals The infection is thus transmitted from vertebrate to vertebrate through at least two generations of mites

Tick-borne In many parts of the world it has been found that a number of diseases bearing a variety of names are due to rickettsial infections conveyed to man by the bites of ticks, the resultant diseases in man may be grouped under the general designation of the tick-borne typhuses The hosts of the rickettsia responsible normally are animals belonging to a wide range of species, and the infections are conveyed from one animal to another by sundry ticks in which they cause a generalized or septicaemic type of infection This means that the salivary glands become infected, so that the tick can infect by its bite, also its ovaries become infected, and the female ticks can pass on their infections congenitally to their offspring through several generations The nomenclature of the causative organisms has not reached finality, but most of them have been grouped into the genus *Dermacentroxenus*, which is distinguished from the genus *Rickettsia* by differentiating features in their morphology, their location in infected cells, and

from man to man

The rickettsias The rickettsias are minute pleomorphic organisms, in zoological status they are intermediate between the bacteria and the viruses They appear as rounded forms 0 3 to 1 0 µ in diameter and rods from 1 5 to 2 5 µ in length, but they vary considerably in form in differing environments They are Gram-negative, but they stain well with the Romanowsky dyes when water adjusted to pH 7 4 is used as a

diluent Most small laboratory animals can be infected with the rickettsias which infect man, but the degree of their susceptibility to the different organisms varies In experimental animals, as in man, the rickettsias live intracellularly and they attack chiefly the endothelial cells lining the smaller blood vessels. They can be cultured in living tissue culture media, and on the yolk-sac membrane of developing chick embryos As a rule they do not survive for long at normal temperatures or at 37° C and are quickly killed by heat and most antiseptics; but in infected louse faeces *R prowazeki* remains viable for months if the temperature and humidity are kept low *R. burneti*, the cause of Q fever, is unusually resistant to heat, to drying and to chemical disinfectants. If subjected to quick freezing in a sealed ampoule and stored in dry ice (−76° C) they remain viable for several years, provided that they are rapidly thawed from the deeply frozen state; slow thawing after a deep freeze kills them

[illegible] has been

sul [illegible]

ge [illegible]

prowazeki is the organism responsible for epidemic louse-borne typhus; it is the only one of these organisms which can maintain itself in man and his own ectoparasites, it requires neither non-human ectoparasites nor other mammals for its survival. *R. mooseri* is a very closely allied species, which morphologically and antigenically is closely similar to *R prowazeki*, it shows certain biological differences from it in that it is normally a parasite of rats and mice, it is conveyed by the rat louse *Polyplax spinulosus* and the rat flea *Xenopsylla cheopis*, and it gains entry only incidentally and accidentally into man It is not normally transmissible by the human louse or the human flea, though both these have been infected with it artificially or experimentally they are not efficient natural vectors of the organism *R. orientalis* (or *tsutsugamushi*), of which there are several antigenic types, is the organism responsible for scrub, or mite-borne typhus, in nature it is a parasite of wild rodents, being conveyed from one to another by mites of the genus *Trombicula* Probably several species of these mites serve as effective vectors, and the two most important which are held to be chiefly responsible for human infection are *T. akamushi* and *T. deliensis* The infection is maintained from one generation of mites to the next by transovarial passage, as each mite takes only a single meal on warm blooded animals a female mite on infection can only infect another mammalian host through its offspring

The genus *Dermacentroxenus* embraces two species, *D. rickettsi* and *D. conori* The former normally affects small mammals and occurs in man only as an accidental infection *D. rickettsi* includes a number of varieties of the species; all are conveyed by ticks, and these transmit the infection

through their ovaries to their offspring As ticks are regular blood feeders they themselves therefore can pass on the infection directly, or they can do so indirectly by its transference to the next generation of ticks. Man is freely attacked by ticks in search of a blood meal and is infected by the bite of an infected tick These organisms are not transmissible by lice, by fleas, or by mites The diseases in man resultant on his infection with them have been called the 'spotted fever' group of typhuses, or tick-borne typhuses The ticks responsible for their spread vary with the locality of the disease; and the latter shows minor variations from one region to another of its incidence Rocky Mountain Spotted Fever, of which there are several varieties, commonly is conveyed by the wood tick *Dermacentor andersoni*; but *D variabilis*, *Amblyomma americanum*, *Rhipicephalus sanguineus*, *Haemaphysalis leporispalustris*, *Ixodes dentatus*, *Ornithodorus parkeri* and *Otocnetor nitens*, together with other species of these genera, in various places and at various times, have been found in nature to be infected with the different varieties of *D rickettsi*

Dermacentroxenus conori is morphologically indistinguishable from *D rickettsi* It has long been known to be transmissible by the common dog tick *Rhipicephalus sanguineus*, which is of worldwide distribution, no mammalian host other than man was proved to be infected with the organism The infection is maintained hereditarily in the tick, and this has been thought to be the sole natural host of the infection The dog does not appear to be a reservoir of the infection, but merely a vehicle for the tick, attempted infection of various rodents and other small animals was unsuccessful Recently, however, *D conori* var *pijperi*, the cause of a tick typhus in South Africa and East Africa, has been recovered from wild rodents and ticks in those areas

THE WEIL-FELIX TEST IN THE TYPHUS FEVERS

In 1915-16 Weil and Felix cultured strains of organisms of the *B proteus* group from the urine of Rumanian cases of epidemic typhus These were found to be agglutinated to high titres by the sera of persons convalescent from the disease The strains were designated Proteus X 1, X 2, and so on, strains X 19 and, to a lesser extent, X 2, were found to be agglutinable to higher titres than the others, and these two have since been maintained in laboratories throughout the world for the performance of the Weil-Felix test They have been dissociated into their O and H variants, and the former of these is now exclusively used for the test in view of its greater specificity

In 1923 a Proteus OX 19 strain was sent from the National Collection of Type Cultures to Malaya, there it is reputed to have undergone some antigenic variation, at any rate, this strain, known as OXK, has

since been found to be specifically agglutinated by the sera of persons recovered from mite typhus, but not by sera of persons convalescent from the other typhus diseases

In the following table are summarized the results obtained by Weil-Felix tests with the three standard strains OX 19, OX 2, and OXK on convalescent sera from cases of the various forms of typhus From this [illegible]

titre, and in the majority of cases of tick-borne typhus OX 19 and OX 2 are agglutinated, though to a low titre only This test is therefore of considerable help in the diagnosis and differentiation of the typhus diseases After the tenth day of the disease agglutinins are present in significant titre in the serum; the titres thereafter continue to rise for a week or ten days, they then gradually diminish to a low level over a period of months It is the rising titre which is of particular help in diagnosis, and therefore the test should be repeated at least once during the development of the disease

Disease	OX 19	OX 2	OXK
Louse-borne } Flea-borne }	+ + + to	+ + to −	−
Tick-borne	− to + +	− to + +	−
Mite-borne		−	+ + +

OTHER SEROLOGICAL TESTS

Means of identifying with some precision the strains and types of rickettsial infections include the agglutination by sera of suspensions of rickettsia, and cross absorption tests, a complement fixation test, using as antigen extracts or suspensions of rickettsia; the passive protection of animals by hyperimmune sera, and a number of special neutralization and antitoxic tests performed on experimental animals after a strain of organisms has been recovered and maintained in culture By these [illegible]

ANIMAL INOCULATION

[illegible]

typhus when inoculated intraperitoneally into a male guinea pig causes fever after about ten days This is due to infection with the causative

organism, *R prowazeki* Blood from cases of murine typhus (*R mooseri*) in addition to fever causes an inflammatory reaction in the tunica vaginalis, from which the organisms can be recovered (tunica or Neill-Mooser reaction) Obtained from cases of tick-borne typhus (*D*

but mice so inoculated become fatally ill, and on autopsy there is a white peritoneal exudate with numerous organisms in the peritoneal cells (peritoneal reaction)

OTHER RICKETTSIAL DISEASES

In addition to the more clearly defined and better known louse-borne, flea-borne, mite-borne, and tick-borne typhus fevers there are a number of other rickettsial diseases of man at present of somewhat less clearly determined status These include Brill's disease, Q fever and atypical pneumonia, Bullis fever, rickettsial pox, and trench or Volhynian fever

In 1898 Brill discovered sporadic cases of typhus in New York which were of a relatively mild type, and which did not spread from the individuals affected, who usually were free from any evidence of louse infestation Subsequently it was suggested that these were cases of murine flea-borne typhus In 1934 Zinsser on reinvestigating cases of

showed that Brill's disease was related to classical louse-borne typhus rather than to murine typhus, and he considered it to be a recrudescence of louse-borne typhus

A condition named Q ('Query') fever was discovered in 1935 among meatworkers in Queensland, Australia Its causative organism was identified and named *Rickettsia burneti* Shortly thereafter this same organism was recovered from naturally infected ticks, *Dermacentor andersoni*, in N America, laboratory workers handling it developed Q fever Outbreaks of this fever were disclosed in meat workers elsewhere in the U S A and its presence is now recognized in many parts of the world, including Great Britain Ticks of several genera are known to serve as vectors, many small wild animals and large domestic animals —cattle, sheep, goats and dogs—and even birds serve as reservoirs of the infection *Rickettsia burneti*, unlike the other rickettsias, is remarkably resistant to heat, to drying and to chemical disinfectants Probably in domestic animals the organism has become adapted to contact infection

in the absence of ticks. Man can acquire the infection from the larger domestic animals by inhalation of aerosols or the consumption of their milk In Great Britain the known incidence of clinical Q fever in males is considerably (12 times) greater than that in females, and it commonly occurs between the ages of 20 and 50. Search for antibodies shows that the incidence of infection in females in Britain is much nearer that in males than the clinical evidence of the disease in them suggests; perhaps women are less susceptible to the disease or they are exposed to smaller infecting doses of the organisms. The incidence of Q fever and its manifestations in inhabitants of the tropics have not yet been determined.

The clinical onset of Q fever is sudden, with severe and increasing frontal headache and retro-orbital pains, shivering attacks, profuse sweating and fever with a relative bradycardia. During the first week about half the patients show signs of pneumonia, which often are limited to a small area of a lower lobe. But X-ray examinations in these cases show the lesions to be more extensive, and one or two large opacities commonly are seen in the middle or lower lobes. Patients without physical signs of pneumonia also will usually show characteristic lung lesions on X-ray examination. The fever and very intense headache, often with rigors and possibly delirium, and in many patients a cough sometimes with haemoptysis, normally continue for one to four weeks; in some few cases the disease persists for months, and in these thrombosis and embolism are important complications In Britain fatalities are unusual and have been the result of pulmonary infarction; mild attacks are usual in epidemics, and subclinical infections occur

The clinical diagnosis of Q fever is confirmed by the X-ray changes seen in the lungs of most patients. Laboratory diagnosis rests on the demonstration of agglutinins for the appropriate killed rickettsial suspensions, a positive complement deviation test with a rising titre; or the recovery of the organism by culture or animal infections This infection does not cause the production of agglutinins for the Proteus strains used in the Weil-Felix test, which therefore is of no help in specific diagnosis

Chloramphenicol and the tetracycline antibiotics are dramatically effective in treatment; penicillin and the sulphonamides are without effect

Bullis fever is possibly a rickettsial disease of man, conveyed by ticks, which occurred as a minor epidemic at a military centre in the U.S A during the Second World War. It was a mild disease showing some differentiating features from the commoner tick-borne typhuses

1946. The causative organism *Rickettsia akari* is transmitted by the mite *Allodermanyssus sanguineus* which infests mice, in which the organism is enzootic

During the static trench warfare of the First World War a great many of the participants on both sides suffered from a condition called trench fever or Volhynian fever This was considered to be due to infection of [illegible]

the Second World War it has been reported that the disease again appeared on a considerable scale among the German troops on the Russian fronts

EPIDEMIC LOUSE-BORNE TYPHUS

DEFINITION

Typhus exanthematicus is due to infection with *Rickettsia prowazeki*. The organism is conveyed from man to man by the human louse *Pediculus humanus* The course of the resultant disease is characterized by a sudden onset, sustained fever, severe toxaemia, a generalized rash which appears about the fifth day, and marked nervous symptoms Its duration is about sixteen days and the mortality is high, especially in some epidemics

GEOGRAPHICAL DISTRIBUTION

Wherever the climatic conditions and state of hygiene favour infestation with the human louse epidemic typhus may appear Such conditions most prevail in the colder parts of the globe, but they are by no means limited to these regions

AETIOLOGY

Throughout the febrile stage of the disease *R prowazeki* is present in the blood of a patient suffering from it The louse *Pediculus humanus* feeds exclusively on man Lice feeding on a patient suffering from epidemic typhus become infected with the causative organism, and after eight to ten days excrete it in their faeces *R prowazeki* in the intestine of the louse enters and multiplies very freely in the cytoplasm of the epithelial cells of its mid-gut The infected cells become swollen and they rupture, liberating the organisms into the faeces, in which they escape to the exterior in large numbers Inunction of the infected

faeces through abrasions of the skin or mucous surfaces, or their inhalation, are the means by which they enter a fresh host

Lice tend to leave the body of persons suffering from high fever, and they also leave the cooling or cold skin of the dying or dead This tendency of the lice to migrate from such persons favours the dissemination of the disease. Inhalation of the dried faeces of infected lice in the dust from linen and clothing of the sick or dead can result in transmission of the disease in the absence of migration of the infected lice On occasions it has been suspected that the organism may remain viable and infective in clothing kept under suitable conditions for many years

R prowazeki can be introduced by inoculation or by insufflation of the lungs into laboratory animals including monkeys, guinea pigs, rats and other rodents In them it usually causes a febrile illness, and during this illness the organism can be recovered from them

Typhus exanthematicus is one of the greatest epidemic diseases of history It has been associated with nearly every great war and famine since the fifteenth century Few diseases can spread through a community or ravage a continent with greater rapidity than epidemic typhus It is a disease of poverty, filth, human distress and overcrowding In the tropics where clothing is scanty or absent louse infestation is unusual. In the very cold climates where clothing is worn for long periods without removal, and people huddle together to keep warm, louse infestation is very prevalent

Infants below five are only slightly susceptible to the disease; in children epidemic typhus is relatively a mild disease; it increases in severity with rising age, until at and over forty years of age the mortality from it is extremely high. One attack of typhus exanthematicus affords a substantial life-long immunity to reinfection, although this is not invariably absolute. Whether the infection always vanishes, or whether it may persist for prolonged periods and result in a state of 'premunization' has not been established It has been claimed on epidemiological and other grounds that Brill's disease (q v.) is a recrudescence, with mild symptoms, of the infection some years after recovery from a primary attack of classical louse-borne typhus

PATHOLOGY

Rickettsia prowazeki parasitizes the endothelial cells lining blood vessels of the skin, the central nervous system, the skeletal muscles and myocardium and, to a lesser extent, those of the kidney, testis and other organs The affected cells become swollen and there is a vigorous proliferation of the vascular endothelium, in which mitotic figures can be seen. This is an endangeitis. Around the affected vessels circum-

scribed groups of proliferating cells appear These are the typhus 'nodules' of Fraenkel, they are composed chiefly of mononuclear phagocytic cells probably of endothelial origin A diffuse perivascular infiltration of mononuclear cells, lymphoid and plasma cells, mast cells and some polymorphonuclear cells is also evident in the skin The vascular damage leads to thrombosis, and to haemorrhage from the vessels, both these are constant features of the pathology of typhus exanthematicus, and they are invariable in the small vessels of the skin, central nervous system and myocardium

These changes extend to larger vessels as the disease progresses In these an occluding thrombosis is rare, but mural thrombi may exist without severe damage to the media of the large vessels

At autopsy there are no gross changes characteristic of typhus exanthematicus, other than skin lesions Petechial haemorrhages in the skin and central nervous system are usual, commonly there are bronchopneumonia and evidence of myocardial changes The spleen usually is enlarged At times there are gangrenous patches of skin and deep sloughs into the subcutaneous tissues and even muscles In some epidemics gangrene of the extremities is common, but this has been attributed to nerve lesions rather than to thrombosis of large vessels

CLINICAL PICTURE

The incubation period can range from 5 to 23 days, usually it is between 8 and 14 days

The onset is abrupt, with the usual manifestations of a very severe febrile toxaemia It is initiated by a rigor or rigors, headache and muscular pains, and a fever which mounts steadily, with occasional remissions, to 103° F or more within a few days, during this period the headache and pains in the back and limbs become more severe The face is flushed and congested, the conjunctivae are suffused, the tongue is furred and tremulous, and the mouth becomes dry, and sordes form on the lips There is nasal catarrh, with reddening of the nasopharynx and of the fauces, pharynx and tonsils Epistaxis is common The respiration rate is increased, and there are signs of bronchitis There is abdominal discomfort, but constipation and not diarrhoea The spleen is palpable by the third day From the patient may issue a distinctive mouse-like odour Deafness is a common symptom After the third or fourth day there is marked torpor, often associated with delirium, the condition now resembles severe typhoid in the third week of the disease

The rash appears about the 5th day of the disease, it shows first on the shoulders and axillae, and it soon spreads to the abdomen, chest, back and extremities, it rarely occurs on the face or on the palms and soles. The rash consists of rose spots, these are not unlike those of

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In favourable cases the temperature begins to fall by rapid lysis on the 12th or 13th day, it reaches normal between the 14th and 16th days, when the attack ends

In fatal cases death usually occurs during the second week, and most frequently between the 10th and 12th days A rising blood non-protein nitrogen, and oliguria, are of bad prognostic significance

Complications Myocarditis is said to be common Gangrene of areas of skin frequently occurs In some epidemics symmetrical gangrene of the extremities is seen in a high proportion of cases, this is now thought to be due to nerve lesions and not to major arterial or venous thrombosis Suppurative parotitis is a common complication.

TREATMENT

In 1942 *para*-aminobenzoic acid, given in large doses by the mouth, was shown to influence favourably the course of experimental *Rickettsia mooseri* infections in mice Numbers of patients suffering from epidemic typhus in Egypt were later treated with initial doses of 4-8 gm of the drug, and subsequently doses of 2 gm two-hourly, by mouth to a total of from 60 gm to over 200 gm Later, typhus patients were treated elsewhere with *para*-aminobenzoic acid, or its sodium salt, by mouth Though the drug beneficially influenced the course of the disease, its action in doing so was slow, and it could not be regarded as specifically curative of the infection Its employment has been superseded by the discovery that some of the antibiotics are much more rapid and efficient therapeutic agents in these diseases

In 1947 it was shown that the antibiotic, chloramphenicol, exerted a marked rickettsiostatic action *in vitro*, it proved therapeutically very effective when used against experimental infections in animals with the various rickettsias causing the human typhus diseases In 1948 human cases of louse-borne and of flea-borne (murine) typhus were treated orally with chloramphenicol with most encouraging results Since that time nearly all types of human typhus have been shown to respond most satisfactorily to chloramphenicol treatment by mouth The tetracycline antibiotics, aureomycin and terramycin, similarly given, have proved equally therapeutically effective in all forms of human typhus

Chloramphenicol is given by the mouth The initial dose in treating typhus is 3 gm, this is followed by 0 25 gm three-hourly for twenty-four hours, smaller doses are then given for another four days In every case of typhus so treated, unless moribund, there is rapid clinical improvement, the fever vanishes, usually within two days, the patients soon become convalescent and recover The immediate side-effects of

typhoid, but they are much more numerous and widespread. They fade on pressure for the first day or so; but later they become dull red in colour and no longer fade on pressure. By about the 10th day of the disease they are brownish red in colour and beginning to disappear. In addition, there is a blotchy eruption, or 'subcuticular mottling'; this also first appears on the shoulders and axillae, and then extends to the chest, abdomen, back and extremities. In very severe cases there may be purpuric patches which sometimes attain a large size. Haematemesis, melaena and haematuria all may be evident in the gravest cases

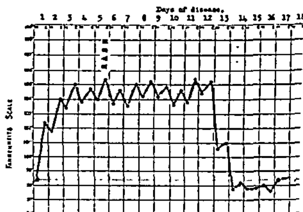


FIG 55 Temperature chart of case of louse-borne typhus. [From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

Nervous symptoms are pronounced, they take the form of dreams of a frightful nature, of tremors and twitching of the muscles (subsultus tendinum), of tremors of the tongue, and of stupor and delirium; they develop during the first week of the disease and are of diagnostic significance In severe cases coma may supervene on the 6th or 7th day, or maniacal symptoms may develop The knee jerks may disappear about the 5th day Incontinence of urine and of faeces may occur on the 6th or 7th day and persist into convalescence. Cerebral involvement [illegible]

rium and meningeal symptoms may simulate cerebrospinal fever; lumbar puncture is then advisable to differentiate between the two

The respiratory system is always involved to a greater or less extent. Bronchitis is often followed by bronchopneumonia, and sometimes by pleurisy or empyema The condition may terminate by abscess or gangrene of the lung

a vaccine for the protection of man without misadventure In the majority of cases it produces a neutralizing antibody which lasts for at least five years, although the complement fixation antibody disappears within one year; in these cases it affords a more efficient and lasting protection against challenge with virulent strains of organisms than do vaccines of the Cox type. Further testing may prove this to be both a safe and effective form of protection for general adoption

FLEA-BORNE TYPHUS

DEFINITION

Murine typhus is due to infection with *Rickettsia mooseri* The organism normally affects rats, from one to another of which it is conveyed by rodent lice and fleas The rat flea *Xenopsylla cheopis* may infest man and convey the infection to him in its excreta The resultant disease clinically is indistinguishable from typhus exanthematicus; but it is much milder and its mortality is low

GEOGRAPHICAL DISTRIBUTION

Flea-borne typhus is world-wide in distribution Various names were applied to it before its aetiology locally was appreciated These include tarbardillo in Mexico, Toulon ship fever, urban tropical typhus or shop typhus in Malaya, and Manchurian typhus, among others Wherever the rat lives in close association with man, irrespective of climate, flea-borne typhus may occur

AETIOLOGY

Strains of *Rickettsia mooseri*, the causal organism, have been recovered from wild rats in many parts of the world In them in nature it is enzootic, causing an apparently symptomless infection It is conveyed from one to another by the rat louse *Polyplax spinulosus*, and by the rat flea *Xenopsylla cheopis* In these ectoparasites the infection is an intestinal one, and the faeces of the infected lice and fleas contain the organism The rat flea *Xenopsylla cheopis* in default of its normal host may temporarily infest man and take a blood meal from him Infection of man is the result of entry of the organism excreted in the faeces of an infected flea through abrasions of the skin, alternatively man may be infected by inhalation of the organism in dust containing infective rat flea or louse faeces In addition to this it has been shown that *R mooseri* is passed in the urine of infected rats, it has been suggested that Toulon ship fever is acquired by contamination of food with infected

chloramphenicol treatment are negligible but jaundice and a fatal aplastic anaemia have on rare occasions followed its use.

Aureomycin or terramycin, which can be used alternatively to chloromycetin, are given in similar dosage

PROPHYLAXIS

All patients and contacts should be completely freed of lice. Clothing and bedding should be immersed in a solution of disinfectant before being sterilized. Cleansing of the surrounding population as a whole, by the use of D.D T. and other insecticides, should be undertaken promptly and vigorously at the outset of a suspected epidemic. By these means epidemic typhus has on several occasions been stamped out on its appearance in a city before it properly gained a foothold and flared up on a grand scale

Personal prophylaxis for those at risk in addition to precautions against louse infestation, such as the employment of insect repellents such as dimethylphthalate and the wearing of protective clothing, is adequately ensured by protective inoculation with a vaccine. In 1924 Weigl made a vaccine from *R. prowazeki*, which he obtained by triturating the intestines of human lice infected intrarectally with the organism The method requires much skill and labour; it consequently is costly, and the amount of vaccine yielded by it is very limited Nevertheless the vaccine afforded very substantial immunity against epidemic typhus.

For some years vaccines prepared from cultures of *R prowazeki* and *R mooseri*, and from the hyperinfected tissues of animals, such as the lungs after infection by insufflation, have been utilized. Cox's vaccine, that at present most used, is made from killed cultures of strains of the two organisms grown on the yolk-sacs of developing chick embryos The vaccine is given subcutaneously in doses of 1 ml on two or three occasions at weekly intervals; reinforcing doses should be given at six-monthly intervals during the period of risk of infection A satisfactory, though not necessarily absolute, protection is afforded against louse-borne and flea-borne typhus by this vaccine immunization If an attack of either develops in spite of the vaccination its severity is much modified as a result of it These vaccines afford no protection against the mite-borne or the tick-borne typhuses.

A strain of *R. prowazeki* (Strain E) of normal virulence, isolated in Spain in 1941, was maintained by egg yolk transfers in the usual way By the sixteenth passage this strain was found to have lost its virulence for guinea pigs and other animals, though retaining its immunizing properties. It remains avirulent At various times, and latterly on a considerable scale in Peru, this living avirulent strain has been used as

MITE-BORNE TYPHUS

DEFINITION

Mite-borne or scrub typhus is due to infection with *Rickettsia orientalis* (or *tsutsugamushi*) The organism normally affects small bush-dwelling rodents and mammals, from one to another of which it is conveyed by trombiculid mites in which it is transmitted hereditarily These mites may attack man and convey the infection to him by their bites The resultant disease clinically in general resembles epidemic louse-borne typhus; but in many minor details it differs from it, notably in the presence usually of an initial eschar The mortality may be high

GEOGRAPHICAL DISTRIBUTION

Scrub fever, tsutsugamushi, Japanese River fever, Sumatran mite-fever, Malayan rural typhus, and other names have been applied to [illegible]

AETIOLOGY

Strains of the causative organism, *Rickettsia orientalis*, have been recovered from many rodents and small mammals, and from several species of trombiculid mites in the enzootic and endemic areas of the Eastern hemisphere The areas in which man acquires the disease are usually very sharply demarcated regions in bush country, where there is sufficient ground moisture for the mites to flourish in association with a suitable population of small mammals Such conditions are found in uncultivated areas of vegetation along river courses The mites principally responsible for conveying the disease from one mammalian host to another are *Trombicula akamushi* and *T deliensis* As already indicated, these mites take but a single meal on mammals during their lives, this meal of blood, lymph, or tissue juice is engorged during the six-legged larval stage A septicaemic infection of the mite with *R orientalis* follows an infected meal on a mammalian host, the infected female mite transmits its infection hereditarily to its offspring, which infect further mammalian hosts by their bites on the occasion of their meals on mammals. The larval mites show a catholic taste in search of this meal, and will attack man as well as other mammals of all sizes Man is a rare and sporadic host of the infection unless engaged in large numbers, such as during war-like or agricultural clearing operations, in

rat urine, as well as by the agency of the rat flea Flea-borne typhus thus occurs as a sporadic infection of man As the human ectoparasites, *Pediculus humanus* and *Pulex irritans*, at best are inefficient vectors of *R. mooseri*, flea-borne typhus does not spread from man to man and *therefore does not become epidemic* As already stated, it has been postulated that occasionally *R. mooseri* becomes adapted to effective transmission by the human louse, and that this is the genesis of epidemic louse-borne typhus

R mooseri is very closely related to *R prowazeki*; it is similar in size, shape, staining properties, and its resistance to chemical and physical agents Its antigenic structure is also very similar to that of *R prowazeki*, though some minor differences have been demonstrated by ex-

[illegible]

and an attack of one of these diseases immunizes against an attack of the other

On intraperitoneal inoculation of *R. mooseri* into male guinea-pigs the tunica or Neill-Mooser reaction results and the animals develop a more marked febrile reaction after the introduction of blood infected with this organism than those with that containing *R prowazeki*. The *human louse, Pediculus humanus, can be infected with R. mooseri* by Weigl's method of intra-rectal injection. Nevertheless the human louse so far has not been effectively infected by experimental feeding on patients suffering from flea-borne typhus.

PATHOLOGY

There is no essential difference in the histopathology of *R mooseri* infections from that seen in *R prowazeki* infections

CLINICAL PICTURE

The clinical picture is that of epidemic louse-borne typhus, except for the mildness of the disease, the infrequency of severe complications and the correspondingly low mortality

TREATMENT

The specific treatment is that of the epidemic louse-borne typhus disease. Specific personal prophylaxis lies in the protection afforded by Cox's vaccine

scab, and commonly is situated on the trunk The lymph glands draining it may be enlarged, not uncommonly there is general lymphatic glandular enlargement The presence of this lesion clinically is of diagnostic importance, and it should always be carefully sought, it is by no means invariably found and appears to be more usual in some areas of endemicity than others Commonly it persists for about three weeks, that is until the disease has run its course

The rash appears between the fifth and the eighth days of the disease as a macular eruption on the sides of the chest and the abdomen, it soon spreads to the extremities as does that of typhus exanthematicus. It persists for some days before fading, and it may then fade rapidly over a few hours

The fever lasts about two weeks, it then falls to normal by slow lysis over several days The symptoms and signs accompanying it are those usual in epidemic typhus Death in fatal cases takes place about the end of the second week, commonly it is attributable to a secondary pneumonia, encephalitis, or circulatory failure The mortality under varying conditions of locality and population ranges from 2 to over 60 per cent

DIAGNOSIS

but not for Proteus OX 19 or OX 2, begin to appear in the patient's serum about the tenth day of the disease, they rise in titre to a maximum by the end of the third week, thereafter they decline in titre to a low level by the sixth week, when they may disappear Repeated tests are advisable to demonstrate the rising titre, the maximum figure it reaches may not exceed 1/160 but the steady rise to this figure is highly suggestive of the diagnosis Though other forms of typhus fever do not give a positive Weil-Felix test with Proteus OXK, it is stated that an attack of Weil's disease (leptospirosis) or of louse-borne relapsing fever may do so

TREATMENT

As for typhus exanthematicus with chloramphenicol or aureomycin

PROPHYLAXIS

Vaccines have been made from *R orientalis*, but none so far produced has afforded adequate protection of man against scrub fever

Communal prophylaxis takes the form of avoidance or destruction of those clearly defined areas of vegetation where the disease is acquired

the jungle foci of infection In the Second World War some thousands of troops engaged in jungle warfare were infected with *R orientalis* and suffered from scrub fever The infection in man nevertheless normally is a sporadic one, it does not spread from man to man directly or through the agency of his normal ectoparasites, the human louse and the human flea. Air-borne infections with *R. orientalis* may occur among laboratory workers insufflating animal lungs with the organisms; not uncommonly they are fatal

Rickettsia orientalis morphologically is rather less pleomorphic than the other species of rickettsias which infect man It lives intracytoplasmically, and it can be seen as bipolar-staining bodies in the cytoplasm of endothelial cells It can be cultured in living tissues, and with some difficulty on the yolk-sac of the developing chick embryo, it can readily be established in laboratory animals, in mice it causes a fatal infection with fever and ascites (peritoneal reaction) when injected intraperitoneally, in rats it produces a symptomless infection unless introduced intravenously in large dosage, when it causes death

Antigenically *R orientalis* is distinct from *R prowazeki* and *R mooseri*, and from the species of *Dermacentroxenus*. In the Weil-Felix test Proteus OXK only is agglutinated. Cross-immunity tests, complement fixation tests, neutralization tests and toxin-antitoxin techniques show not only its clear differentiation from other species of *Rickettsia*, but the existence of antigenically different strains of *R orientalis* This antigenic variation between strains of *R. orientalis* contrasts with the antigenic homogeneity of all strains of *R. prowazeki*

PATHOLOGY

The histopathology of scrub fever broadly conforms to that of epidemic louse-borne typhus At post mortem a primary eschar commonly is seen, but the rash usually is not evident The lesions of the small vessels as a rule are less pronounced than in epidemic typhus A specific rickettsial toxin is formed by *R orientalis*; the action of this toxin on the peripheral capillaries, together with the characteristic capillary and vascular pathology, is thought to be responsible for the peripheral circulatory collapse which contributes to death in a high proportion of fatal cases of scrub typhus

CLINICAL PICTURE

The incubation period is six to eighteen days The onset resembles that of epidemic typhus, but there is a primary lesion or eschar at the site of infection by a larval mite. This appears before symptoms develop This eschar is a small necrotic ulcer covered with a blackened

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invasion is seen not only in cells in artificial cultures, but in the tissues of animals infected with the organisms

The tick typhus due to *D rickettsi* in the Americas affects chiefly rural populations, especially those whose outdoor work brings them into contact with wild life and with tick-infested stock or pastures Hunters,

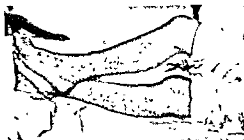




FIG 56 (a and b) The rash of tick-borne typhus
[Courtesy of Col B Blewitt, R A M C]

trappers, campers, and others often acquire it when following their pursuits, but women and children largely confined to the precincts of a house may be infected by ticks brought in on dogs and household animal pets

D rickettsi var *pijperi* is the name given to a similar organism which causes 'tick-bite fever' in South Africa, a mild form of tick-borne typhus with a low mortality The animal reservoir of this organism has not been determined, but the disease occurs sporadically among

Personal prophylaxis, when the areas cannot be avoided, lies in active movement through them, and the wearing of protective apparel dressed with insect repellents such as dimethylphthalate.

TICK-BORNE TYPHUS

DEFINITION

The tick-borne typhuses are due to infection with species of rickettsias of the genus *Dermacentroxenus*. These organisms normally are enzootic in a wide variety of animals. They are conveyed from one animal to another by a number of ticks of different genera and many species Man is infec[illegible]
him The course of [illegible]
epidemic louse-borr[illegible]
mortality varies with the local variations in the disease; in some it is high.

GEOGRAPHICAL DISTRIBUTION

Various forms of tick-borne typhus have been identified in each of the continents of the world. These include the Rocky Mountain spotted fevers of North America, the spotted fevers of South America, the *African and the Indian tick-bite fevers, North Queensland tick-typhus,* and Fièvre boutonneuse of the Mediterranean regions

AETIOLOGY

Dermacentroxenus rickettsi, the causative organism of the various types of Rocky Mountain spotted fever, and the spotted fevers of South America, in nature infects a very varied assortment of small wild mammals in which usually it causes a symptomless infection A large number of ticks of various genera and species have been found to serve as efficient vectors of the organism In these when taken up in a blood meal it causes a generalized infection; the ticks after a period can infect by their bites, and the female ticks transmit their infections hereditarily

[illegible]

cytoplasm, as are organisms of the genus *Rickettsia*. This intranuclear

invasion is seen not only in cells in artificial cultures, but in the tissues of animals infected with the organisms

The tick typhus due to *D rickettsi* in the Americas affects chiefly rural populations, especially those whose outdoor work brings them into contact with wild life and with tick-infested stock or pastures Hunters,

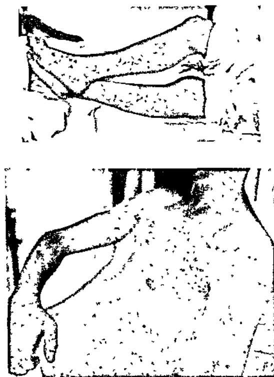


FIG 56 (a and b) The rash of tick-borne typhus [Courtesy of Col B Blewitt, R A M C]

trappers, campers, and others often acquire it when following their pursuits, but women and children largely confined to the precincts of a house may be infected by ticks brought in on dogs and household animal pets

D rickettsi var *pyperi* is the name given to a similar organism which causes 'tick-bite fever' in South Africa, a mild form of tick-borne typhus with a low mortality The animal reservoir of this organism has not been determined, but the disease occurs sporadically among

persons in veldt country Clinically it resembles Fièvre boutonneuse, but a strain of the organism has been recovered from a naturally infected dog, and the organism can be introduced into and maintained with ease in some experimental animals. There are antigenic differences between *D. rickettsi* var. *pijperi* and *D conori*, and the relationship of the former to the *D. rickettsi* of the Americas appears to be a close one. The strains of *D. rickettsi* recovered in north Queensland show certain clear antigenic distinctions from those of this organism recovered elsewhere

Dermacentroxenus conori, as already indicated, much resembles *D rickettsi* but no naturally infected mammal, other than man, has so far been identified Laboratory and other animals are refractory to experimental infection with it. The dog tick, *Rhipicephalus sanguineus*, is its only known arthropod vector; it has been postulated that the organism can survive hereditarily in this tick without any mammalian reservoir of infection

PATHOLOGY

In tissue cultures and in the tissues of infected animals *Dermacentroxenus rickettsi* can be found sparsely in the cytoplasm of the infected cells, but in great numbers in their nuclei. There may be solid masses of the organisms which often entirely fill and greatly distend the nuclei

The histopathological lesions produced by *D rickettsi* are similar to those of typhus exanthematicus There is endothelial proliferation of capillaries, arterioles and venules but Fraenkel's typhus nodules are less pronounced In addition, thrombo-necrotic lesions are prominent and are characteristic of *Dermacentroxenus* infections These are due to the presence of fibrinous thrombi in arterioles and venules, which may be partially or wholly occluded by them In late lesions the vessel wall is infiltrated with endothelial cells and polymorphonuclear leucocytes, and numerous organisms can be seen in the smooth muscle cells as well as in the endothelial cells of the vessel wall The lesions in this disease are a destructive panangeitis of peripheral vessels in contrast to the purely proliferative endangeitis of typhus exanthematicus

At autopsy extensive haemorrhages, and gangrenous sloughing of the scrotum, prepuce, vulva, fingers, toes, or lobes of the ears, are common in the severer forms of the tick-borne typhuses

CLINICAL PICTURE

The severity of attacks of the tick-borne typhuses ranges from mild attacks in ambulatory patients to fulminating attacks with early death. Most cases fall between these extremes, and their general progress much

resembles that of classical louse-borne typhus The main differentiating features are the duration of the fever, the time of appearance of the eruption, and its distribution

The incubation period ranges from two days to two weeks, but commonly is one week The onset is similar to that of the louse-borne disease. The marked remissive fever steadily mounts into the second week of the diseases, it continues until about the end of the third week when, as in the louse-borne disease, it declines by rapid lysis

A rash which resembles the mottling of early measles appears on the third or fourth day This fades and is succeeded by a rose spot eruption which appears first on the wrists and ankles, and then extends rapidly over most of the body including the palms and soles, and the scalp, and sometimes the eyelids and mucosae of the mouth and throat The abdomen and face are the areas last and least affected The spots at first are less pronounced during the morning periods of remission of the fever, but they become progressively more prominent until they are petechial. In severe cases they become a purplish red and confluent, and then they often become necrotic

Sloughing and necrotic lesions of the skin, of the genitalia, and of the extremities are common in the severer forms of Rocky Mountain spotted fever

Fievre boutonneuse, the result of infection with *D conori* is characterized by the presence of a primary sore (tache noire) at the site of the infecting tick bite The rose spot eruption in this disease extends to the palms, the soles and the face This form of tick-typhus is comparatively mild, and the mortality from it is low

DIAGNOSIS

This is apparent on the history and clinical findings in the known areas of endemicity of these diseases In regions where other forms of typhus also occur their differentiation on clinical examination is difficult The Weil-Felix test may be of help in distinguishing them, but it is not specific and may be misleading. The complement fixation test is of greater value in identifying the spotted fevers Recovery of a strain of the organism by guinea pig inoculation and the various detailed serological studies, where these can be performed, are of specific value in diagnosis and identification

TREATMENT

A hyperimmune serum has been prepared from rabbits for the treatment of Rocky Mountain spotted fever If this is given during the earliest stage of the disease, before the third day of the rash, it modifies

its course and reduces the fatality rate *Para*-aminobenzoic acid or its sodium salt, also if given early, influence its course favourably.

Chloramphenicol or aureomycin, however, as used for other forms of typhus, act dramatically and specifically in cutting short the disease

PROPHYLAXIS

In the regions of endemicity the destruction of ticks by burning infested vegetation, dipping stock, and destroying the wild hosts of the tick lessens the risk of infection. The early removal of ticks from the body and cauterization of the site of the bite is of much value in forestalling infection, as ticks do not infect usually until attached for some hours Vaccines prepared from the tissues of infected ticks have been in use for some years The injection of these affords a substantial protection against infection with *D. rickettsi*. Vaccines prepared from growths of the organism on the yolk-sac tissues of developing chick embryos are now available (Cox's method) and are of equal value to those made from ticks for personal prophylaxis. The vaccines are given subcutaneously or intramuscularly on three occasions at about weekly intervals The inoculations should be repeated annually in the spring, before the time of greatest activity of ticks, as the protection they confer does not last more than a year

XI.

ULCERATING GRANULOMA OF THE PUDENDA

DEFINITION

GRANULOMA VENEREUM, or ulcerative granuloma is a venereal disease of unknown causation It is characterized by chronic progressively extending superficial granulomatous ulceration of the genito-inguino-crural regions

GEOGRAPHICAL DISTRIBUTION

Of world wide distribution in the tropics and subtropics, ulcerating granuloma of the pudenda does not occur in the temperate and cold parts of the globe

AETIOLOGY

The causal agent is unknown, but inclusions resembling a short bacillus with rounded ends measuring about 1 μ to 2 μ are constantly found within endothelial and large mononuclear cells in scrapings of the lesions of skin and mucous membranes The exact nature of these inclusions, which are known as Donovan bodies, is still a matter of doubt, their successful culture on special media is stated to have been achieved The condition is usually transmitted by venereal contagion

The disease appears to be limited to warm climates It is much more common among coloured races than the white, and is said to be more common in women than men. The greatest incidence of the disease is in the period of greatest sexual activity

PATHOLOGY

Sections of the spreading edge of the skin lesion show an infiltration of the superficial portions of the corium and of the papillae by lymphocytes There is also a proliferation of the epithelial cells of the interpapillary processes of the rete mucosum, which are prolonged downwards into the corium The corium is highly vascularized In older portions of the lesion there is marked tendency to the formation of fibrous tissue, with the production of scars which break down easily

CLINICAL PICTURE

The initial lesion consists of a papule or vesicle, and in the great majority of cases is found somewhere on the external genitalia, usually

the penis or labia minora, within about a week of sexual contact. The lesion remains superficial and spreads centrifugally, and by auto-infection to opposing surfaces. It exhibits a predilection for moist warm surfaces, particularly the penis and scrotum in the male, the labia, fourchette and vagina in the female, and the inguinal folds, the perinaeal and perianal regions in both sexes In some cases the skin of the face and the mucous membrane of the mouth may be affected, in addition to genital and groin lesions

The disease extends so slowly that years may elapse before a large area of skin is involved, but in mucous membranes the spread is more rapid

Three clinical types of lesions have been described (1) a nodular dry type; this is characterized by a painless granulomatous area raised above the surrounding skin and studded with nodular or sometimes papillomatous dry granulations; this is the commonest type: (2) an *ulcus molle* type; in this the ulcer is large and spreading; it has a depressed base, thin edges and a glazed, moist pale-red surface almost devoid of granulations; there is an offensive discharge and the condition is painful (3) a sclerotic type; this is characterized by the formation of much hard fibrous tissue. Islands of active disease become surrounded by the rapid formation of fibrous tissue, and consequently breaking down of the scar is frequent

Owing to cicatrization, pseudoelephantiasis of the female genitalia, [illegible]

unaffected provided complications arising from strictures of the urethra do not occur.

DIAGNOSIS

This depends upon the great chronicity of the superficial granulomatous condition occurring in the genito-inguino-anal region, and upon the absence of enlarged lymphatic glands Donovan bodies can constantly be found on biopsy of the lesions, or on examination of the exudate from them

TREATMENT

The specific action of tartar emetic in this condition was first demonstrated by Aragao and Vianna in 1913 Subsequently it was largely replaced by various aromatic pentavalent antimonial compounds, and particularly by Neostibosan The drug should be given intravenously in doses of 0 2 to 0.3 gm for an adult The injections should be repeated daily or on alternate days until eight or twelve

have been administered Another drug with which excellent results are stated to have been obtained is the organic trivalent antimonial Fouadin This drug, which is put up in ampoules containing an isotonic 6 3 per cent solution, should be given intravenously in doses commencing with 1 5 cc and increasing to 5 0 cc on alternate days until twelve to eighteen injections have been administered Owing to the great chronicity of the condition and the tendency of the lesions to break down, it is often necessary to give several courses of injections of either of the above.

The antibiotic, streptomycin, is reported to be specific in the treatment of this condition The dosage advocated is 4 gm daily for five to ten days. Chloramphenicol, 0 5 gm six-hourly to a total of 40 gm, is said to be effective, satisfactory results have also been claimed for treatment with aureomycin

An antiseptic dressing should be applied to the lesions. Certain cases are apparently resistant to treatment and in these X-ray applications or diathermy may be tried. In certain cases where there are fistulae, strictures and deformity, surgical interference may be necessary

XLI

THE UNDULANT FEVERS

DEFINITION

THE undulant fevers of man are diseases due to infection with one or other of the species of bacteria belonging to the genus *Brucella* These organisms commonly affect a number of the larger domestic mammals; the infection is acquired incidentally by man through the consumption of infected milk or unfermented milk products, by handling infected carcases, the infected aborted products of conception, or the resultant uterine discharges The diseases are characterized by recurring waves of pyrexia, with intervening apyrexial periods, during which there is toxaemia, enlargement of the spleen, and mild inflammatory lesions of various organs They cause great debility Their course is indefinite but usually is protracted; the associated mortality usually is low

GEOGRAPHICAL DISTRIBUTION AND AETIOLOGY

History Undulant fever in man was first clearly recognized as a clinical entity in the Mediterranean in the middle of the nineteenth century, when many of the British forces in that region suffered from it. It was named Mediterranean or gastric remittent, and later Malta, fever A causative organism, now known as *Brucella melitensis*, was first recovered and isolated from the spleen and the blood of sufferers from the disease by Bruce in Malta in 1886 He succeeded in reproducing the disease by inoculation of this organism into monkeys Nearly twenty years later it was found that *Br melitensis* was present in the [illegible] of a [illegible] in of [illegible] o be infected goat's milk, and in 1906 prohibition of the consumption of [illegible]

[illegible] south-eastern France *Br melitensis* infections of man were derived not only from goats but from sheep, the latter there being an important vector Later still it was shown that cattle became infected with this organism when in contact with infected sheep and goats Thus man might acquire *Br melitensis* infection from goats, sheep or cattle. The mode of acquisition was usually by the consumption of infected milk in the case of goats and of cattle, but more commonly by contact with

infected membranes and uterine discharges in the case of sheep, in the latter case it was the peasant farmers who particularly suffered

In 1897 Bang, in Copenhagen, when investigating contagious abortion of cattle isolated the causative organism which he called *Bacillus abortus* Contagious abortion of cattle is a disease of world-wide distribution and great economic importance, at that time its presence was not considered to be associated with any human malady In 1918, twenty-one years after Bang's discovery, Alice Evans in the United States drew attention to the close similarity between *Br melitensis* and Bang's bacillus, and she suggested that the latter might also be found to infect man In 1921 Bevan in Rhodesia, where contagious abortion of cattle was prevalent, demonstrated a high titre of agglutinins for *Br abortus* in the serum of a patient suffering from undulant fever It was soon shown in many parts of the world that *Br abortus* infections of man did indeed occur, and that these were almost invariably of bovine origin (Thus the occurrence of two forms of undulant fever in man was established, that due to *Br melitensis* infection which classically is acquired from goats, and that due to *Br abortus* infection which commonly is acquired from cattle)

Species Since then a third species, *Br suis*, which normally affects swine, has been found to cause undulant fever in man, furthermore, it has been clearly shown that *Br melitensis*, *Br abortus* and *Br suis* all may infect cattle, sheep, goats or swine, and that man may become infected with any one of them from any of these animals Nevertheless a *Br melitensis* infection of man most commonly is derived from the goat, principally in the Mediterranean, a *Br abortus* infection of man from the cow, in any part of the world, and a *Br suis* infection of man from the pig, chiefly in North America and in Denmark

The differentiation of the three species of the organisms is difficult, and it is made only by skilled bacteriological examination Another organism, *Bacterium tularense*, which produces a disease of rodents in North America, is closely allied to them, this organism does not cause undulant fever in man but tularaemia, a severe plague-like disease conveyed from rodent to rodent, and from rodent to man, by ticks Though causing a clinically distinct syndrome, infection with it may lead to some confusion as it produces cross-agglutinins between itself and the brucella group

Infection of cattle, goats, sheep and swine with the brucella group of organisms is manifested initially by abortion, but there is no evidence that human infection results in this In stock it is particularly the recently infected females that abort In cattle the abortions occur between the fifth and seventh months of pregnancy, the general health of the animals is not affected Subsequently the tendency to abortion lessens until it finally disappears after several pregnancies, but the

animals still are infected with the organism and are a source of infection to others. In addition to a uterine infection infected females suffer from a mild chronic mastitis and excrete the organisms, often in large numbers, in the milk They also excrete it in other secretions and discharges, such as the urine The infection readily spreads from animal to animal by contamination of food and litter, or of grass in pastures, particularly by the infected foetal membranes and uterine discharges from animals which have aborted This material contains enormous numbers of the organisms. The species of *Brucella* are very resistant to environmental change and remain viable for long periods For example, they survive for 42 days in water, 72 days in damp sterile soil, 20 days in manured soil, 28 days in dry road dust, 80 days on dry cloth, and [illegible]

swallowed, or it can enter through abrasions of the mucosal surfaces or of the skin The male animal may become infected through penile abrasions, and subsequently may infect further females in the herd.

Other animals occasionally found to be infected with organisms of the brucella group include horses, dogs and chickens. In horses a brucella infection causes 'fistulous withers' or 'poll evil'.

Incidence Infection of man can result from the practice of 'wet milking', that is wetting the hands with milk before milking. Commonly it occurs in rural populations among cow herds, farmers, veterinarians, and others tending infected stock; it is prevalent among slaughtermen handling infected carcases In urban populations it occurs as a result of the consumption of infected milk and milk products, such as ice-cream, butter and unfermented cheeses There is a significant age and sex distribution of the undulant fevers in man. It is rarely encountered under the age of 15 years, and it is about three times as common in men as in women The incidence seems to be greatest among middle-aged males, children and women past puberty enjoy resistance to the infection, or at least to its clinical manifestations

PATHOLOGY

The organisms on entry into the body are carried to the lymph glands, which seem to be a principle focus for the establishment of the infection They periodically escape into the blood stream and are carried to all parts of the body They may flourish in any of the internal organs, and cause mild non-suppurative inflammatory changes in them At autopsy these changes may be evident in the spleen, which usually is soft and swollen, in the liver and the kidneys, in joints and tendon sheaths, in nerve tissues, in the diaphragm, in the

thyroid gland and in the serous membranes, to mention only some of

standing infections are the uterus, the mammary glands, and their associated lymphatics In the udder of an infected goat, for example, there is a chronic mild mastitis associated with the continuous or intermittent excretion often of enormous numbers of the organisms in the milk secretion over very prolonged periods The same obtains in the case of cattle In women mastitis is unusual and, as already stated, in them abortion is not a direct result of a brucella infection In male animals the seminal vesicles, epididymis and testicles may be similarly involved, and large numbers of organisms sometimes are found in them The urine contains organisms which escape from the infected kidneys It is exceptional for suppuration to supervene in the inflammatory lesions due to a *Brucella* infection, one of the exceptions in the case of man is the development of a form of cold abscess which sometimes occurs over the costochondral joints, particularly in cases of *Br melitensis* infection

initial culture, and the growth is very slow *Br abortus* is most readily cultured under an increased tension of carbon dioxide and a reduced oxygen tension Differentiation of the species by culture is made on slight differences in their biochemical reactions, and by the selective inhibitory actions of a number of dyes These differences are not absolute and require skilled appraisal

CLINICAL PICTURE

The incubation period is difficult to establish with certainty, but it probably ranges from six days to over a month It is generally thought that infection of man by the oral route is followed by an incubation period of from two to four weeks

The onset is gradual, the earlier manifestations are those of any fever, general malaise, headache and retro-orbital pain, generalized muscular pains, and mild gastrointestinal disturbance These are followed, often

fever is of more insidious development During the pyrexial period there is a marked increase in the severity of the earlier symptoms, drenching sweats are a prominent feature, and there may additionally

be severe joint pains The temperature characteristically is of the remittent type, in the early afternoon it rises abruptly a couple of degrees, and it subsides again after several hours only to recur each successive day As a rule during the attack this daily remittent temperature steadily mounts over a period; then, more rapidly, it declines until the patient becomes afebrile The afebrile intermission which follows may last only a few days before it is followed by another similar pyrexial period, it is from this undulatory course that the condition derives its name

The physical signs during the early attacks of pyrexia are not distinctive, but each attack is accompanied by enlargement and tenderness of the spleen, and to a lesser extent of the liver These organs, especially the former, are usually readily palpable when the condition has progressed for some weeks The generalized joint and muscle pains may be severe, there is constant headache, and there often are attacks of peripheral neuralgia Drenching sweats, marked constipation, flatulent abdominal distension and abdominal discomfort are *almost invariable in cases other than the mildest. There is an increasing* normocytic or microcytic hypochromic anaemia, with a marked polymorphonuclear leucopenia

The severe aches and pains cause insomnia and mental depression, and the physical and mental debilitation resultant on the condition are considerable

In Kenya both *Br abortus* and *Br melitensis* infections occur The former is more usual in Europeans, the latter in Africans under 20 years of age — presumably a consequence of their work as goat herds In addition to the classical type of the disease already described, in this area there are types in which either arthritis or gross splenomegaly are the predominant features In the former type it is usually a monoarthritis, but there may be a polyarthritis or an osteitis of vertebrae In the latter type marked splenomegaly is associated with a clinical picture much resembling that of kala azar, with which it is liable to be confused in certain regions In neither of these types is fever the outstanding manifestation, as in the characteristic form of the disease

Complications Many complications of a chronic inflammatory nature may occur, they include arthritis with effusion, and neuritis, less commonly bronchopneumonia, myocarditis or endocarditis; very occasionally, serous effusion; in the male orchitis and epididymitis, and very rarely in women ovaritis and mastitis In severe cases haemorrhages, particularly epistaxis, may occur and sometimes are troublesome; grave toxaemia with purpuric eruptions in the skin and mucous membranes are seen in very severe cases

Severity Cases of undulant fever vary greatly in severity, they range from a mild ambulatory type with few symptoms and signs, through a

more acute form to those with a high remittent fever, and there is a malignant fulminating type which speedily terminates fatally The symptoms and signs due to a *Br abortus* infection are, on the whole, considerably more mild than those resulting from a *Br melitensis* infection It is unusual for a *Br abortus* infection to cause symptoms for more than nine months to a year, but one due to *Br melitensis* often continues to do so for a longer period It has been stated that symptoms of the infection, in the form of recurrent pyrexial waves, may persist for as long as thirty or forty years, but clear bacteriological proof of a persisting infection of this duration is not forthcoming As the disease runs its course lassitude and physical debility become pronounced, and convalescence, when the attacks diminish in severity and duration and finally cease to recur, is prolonged

LABORATORY DIAGNOSIS

Culture The causative organism can usually be recovered from man by culture of the blood under suitable conditions during the febrile periods The attempt to isolate the organisms by this means should preferably be repeated on several occasions The cultures should be incubated at 37° C under a raised CO_2 tension, and they must not be discarded under less than a month's observation Similarly, organisms may be recovered by spleen puncture, by puncture of lymph glands or of the sternal marrow, from the urine or faeces, and possibly from other sources

Serum Examination of the blood serum for agglutinins is of much help in diagnosis, especially when the infection is of some weeks duration. The titres obtained with a suitable antigen commonly rise only to between 1/100-1/500, they may in some cases be considerably higher Sometimes the titre of agglutination does not rise above an insignificant level It is important always to put up a wide range of serum dilutions when performing the test, zones of inhibition commonly are encountered in the lower dilutions, and a negative result in the latter if relied upon will be grossly misleading A complement fixation test has also been elaborated, but this becomes positive later than does the agglutination test The reaction is a group one and must not be relied on for determination of the species of organism causing the disease

Blood picture The blood picture affords information of much confirmatory value in diagnosis There commonly is an anaemia, usually hypochromic or normochromic and rarely hyperchromic, which, particularly in cases of *Br melitensis* infection, may become pronounced before convalescence is established There is an associated lymphocytosis, which may be relative or absolute and is associated commonly with a polymorphonuclear leucopenia

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XLII

VIRUS FEVERS, INCLUDING YELLOW FEVER

INTRODUCTION

FEBRILE illnesses of short duration presumably due to virus infections are common throughout the tropics In some instances the clinical picture is reasonably identifiable and the causative agent known, in others there is clinically little more than fever and the agent has not been identified Accounts are given below of some of the better known infections It should be remembered that many other serious virus infections may occur in both temperate and tropical regions Forms of arthropod-borne encephalomyelitis are common in the Far East Influenza may appear anywhere, sometimes, as recently, in pandemic form Poliomyelitis is very common in many African territories and is at present especially prominent in young adult Caucasians, a high proportion of the indigneous population may possess immunity from early childhood In investigating the cause of any acute febrile illness, these more cosmopolitan infections must always be considered

In the future it is probable that more of the pattern of virus diseases in man and animals will be disclosed In the meantime it is important to remember that these infections exist, since febrile episodes, especially those lasting only a few days, are all too commonly labelled as malaria without further investigation

YELLOW FEVER

DEFINITION

An acute infectious disease caused by a filterable virus transmitted by certain genera of culicine mosquitoes It is endemic in parts of Africa and tropical America Severe cases exhibit fever, with relatively slow pulse, early and progressive albuminuria, vomiting, some jaundice, and varying degrees of hepatic, renal or vascular failure

DISTRIBUTION

The vector mosquitoes are much more widely distributed than the disease, which occurs irregularly over wide areas of Africa and America,

Sensitization An intradermal test using as antigen 'brucellin', a Seitz filtrate of a *Brucella* culture on liver broth, is performed by injecting 0.1 ml of the antigen into the skin The appearance of a raised reddened oedematous area, 2 to 6 cm in diameter, 4 to 38 hours later constitutes a positive reaction In most cases of brucellosis the reaction is positive, but false positive reactions have been recorded in the uninfected A negative reaction is strongly suggestive, though not proof, of the absence of the infection. This reaction is also a group, and not a species, reaction.

TREATMENT

Claims have at various times been made that a wide variety of drugs influence the course of a brucella infection; most of these have not been substantiated and may now be disregarded

Various vaccines, some of them effective prophylactics when given to those at risk, have been given during intermissions of the disease with a view to stimulating antibody formation and so spontaneously bringing the infection to an end Brucellin has been injected to the same end. The value of these measures in treatment is dubious.

The sulphonamides when given in toxic doses may eliminate a *Br. abortus* infection of guinea pigs. In human cases they have proved disappointing and of little therapeutic value. It has been stated that the therapeutic action of sulphonamides on the organisms is reinforced by the additive effect of injection of a weak anti-serum, such as normal human blood There are some unconvincing reports of the successful [illegible]

fically arrests an attack of the undulant fevers due to any of the three causative organisms, the symptoms and signs rapidly disappear, but relapse occurs subsequently in a proportion of the cases so treated The subsequent relapses respond as readily to a repetition of antibiotic treatment as does the attack first treated; there is no evidence of the development of resistance by the organism to the drug. An effective dosage of the tetracycline antibiotics is 0.5 gm six-hourly for ten days; this is repeated in the event of relapse

The vector becomes infected by sucking infective blood from a human or animal case. In man the virus is present in the peripheral blood for about three days after the onset, and probably for a day or two before

The mosquito does not become infective for 12 days to 3 weeks after ingesting the virus-containing blood (the so-called extrinsic incubation period) It subsequently remains infective for the rest of its life The life span of the vector is about 3 months, so that the maximum period of infectivity in individual insects is unlikely to exceed two months This is an important factor in the epidemiology of the disease

EPIDEMIOLOGY

Yellow fever is divided epidemiologically into urban, rural and jungle varieties, which immunologically and clinically are all the same, but which differ in regard to vector and source of infection

In urban yellow fever the reservoir of infection is man, and the vector exclusively the domestic breeder, *Aedes aegypti* In the rural disease the reservoir is man and the vector usually but not always *A aegypti* In jungle yellow fever the reservoir is not man but certain forest animals, notably primates, and the vectors are various species of *Aedes* (other than *A aegypti*) and *Haemagogus* mosquitoes

TRANSMISSION

The successful transmission of urban or rural yellow fever depends on a constant supply of active vectors, the existence of infective reservoirs and the presence of suitable non-immune hosts

When conditions are favourable and the latter are in good supply, epidemics may develop Unless the supply of non-immunes is kept up, however, the epidemic will die out as the survivors become immune

In endemic areas the infection is kept going mainly through young children or non-immune visitors Infants are not easily infected, possibly because of some immunity acquired from the mother Adults native to the endemic areas are commonly protected against reinfection as a result of infection during childhood

The vector of urban yellow fever, *Aedes aegypti*, is found in and about human dwellings It breeds in small collections of water lying in artificial containers tree holes, etc In warm moist conditions breeding and transmission will continue the year round Where rains and dry seasons alternate, transmission is seasonal and at its maximum in the rains The mosquito is killed by cold or desert conditions, but probably [illegible]

regions and is transmitted to man by accident probably during

interior of Colombia and Brazil It is believed to be endemic amongst animals in the forests of the Amazon valley, spreading thence to man from time to time It is now rarely met in Central America, but a few cases were reported recently in Trinidad, from which it had been absent for many years It has been reported in many parts of West and central Africa, within an area ranging from Senegal to the Belgian Congo Immunity surveys have disclosed that the disease is *much more widely spread than was formerly realized. Indications of* fresh infection have been reported in the last decade in Kenya, Uganda, [illegible]

[illegible]

is enzootic in monkeys

AETIOLOGY

Yellow fever is caused by a very small filterable virus measuring about 20 mμ In the human case the virus is present in the blood up to the fourth day of the disease, and can be transmitted by blood inoculation to rhesus monkeys in which it causes a condition similar to the human disease It can be successfully passaged intracerebrally in mice After repeated passage it eventually becomes changed so that although it will continue to cause encephalitis in mice it will no longer reproduce the disease in monkeys or man This altered neurotropic virus is the basis for the production of living attenuated vaccines The virus can be grown in culture provided living cells are present. It is killed rapidly at room temperature but survives for long periods if frozen and desiccated

IMMUNITY

A very powerful and long lasting immunity is set up after an attack of yellow fever or successful vaccination, which affords protection against further attacks

There is some cross immunity to yellow fever engendered by certain other viruses which may exist in a community in which yellow fever is endemic *Infection with some of these viruses may also lead to stimulation* and acceleration of the production of immune bodies on infection with yellow fever Factors such as these probably account for the mildness of yellow fever attacks in individuals, especially children, living in endemic areas

THE VECTORS

Females of several genera and many species of culicine mosquitoes can transmit the virus under laboratory conditions The important natural vectors are certain species of *Aedes* and *Haemogogus*

The cytoplasm of the degenerating cells is acidophil and stains pink

they do in fact occur in coagulative degeneration. As the disease progresses the degeneration becomes more extensive, necrosis occurs and the cells disintegrate. In the late stages practically the whole lobule may become involved.

Changes may also occur in the nuclei. The chromatin concentrates against the nuclear membrane and in some cases nuclear inclusions called *Torres bodies* become visible. These are composed of irregular masses of minute eosinophilic dots occupying the bulk of the nucleus.

Coagulative degeneration occurs in most cases. Nuclear inclusions may or may not be present. In some outbreaks they may appear in a high proportion of cases, in others they may be few or absent. They are a characteristic feature of the pathological picture in laboratory yellow fever in rhesus monkeys. It is believed that they are related to the presence of the virus.

In surviving cases resolution appears to be rapid and complete. No permanent hepatic insufficiency is left and there is no residual cirrhosis.

CLINICAL PICTURE

Incubation Period. The intrinsic incubation period, that is, the time elapsing between the infection and the onset of the disease, varies from 3 to 6 days, with a maximum of 10 days.

In active endemic areas most cases are clinically mild and go on to complete recovery. This is also true of epidemics. Severe and fulminating cases are relatively uncommon.

Mild cases account for the majority of immune individuals found during surveys.

The mild cases may pass practically unnoticed. There is, however, usually severe headache and some fever, conjunctival injection and sometimes epistaxis. Some nausea and bilious vomiting are common. Albuminuria is present from the outset. There is complete recovery in 3 or 4 days.

In more severe cases the fever starts abruptly, sometimes with rigor, reaching 103° to 104° F and falling to normal in 3 to 4 days. The temperature falls more slowly than the pulse, which is initially fast.

The patient complains of severe frontal headache, backache and bone and joint pains. The skin is congested, especially on the face. The conjunctivae are often intensely injected and there may be epistaxis. There is nausea almost from the beginning and often severe bilious vomiting. The liver is not palpable, but epigastric tenderness

epizootics. In Uganda, for instance, the disease is passed from monkey to monkey by *A. africanus*, which normally exists only at high levels in the trees and is thus very unlikely to transmit the infection to man. The spread to humans probably occurs as a result of the accidental infection of some other vector infesting the forest margins, such as *A. simpsoni*, from an infective monkey descended from the forest. In other forest regions, for example, in Brazil, the disease is transmitted from animal to animal by mosquitoes which during the day are found chiefly in the treetops but which may descend at night to ground level and transmit direct to man. Once the disease has become established in humans it may be transmitted cyclically by vectors including *A. aegypti* and even become epidemic

PATHOLOGY

Morbid Anatomy· There is nothing specific about the macroscopic appearance of the body Rigidity and *livor mortis* appear early The blood is fluid The skin becomes yellower as the dissection proceeds and blood drains from it. Jaundice is minimal in fulminating cases, more obvious in the more prolonged cases. The subcutaneous fat is very bright yellow There may be petechial haemorrhages beneath the skin and mucous membranes, and under the pleura, peri- and endo-

[illegible]

in size and yellow brown in colour. Occasionally in very acute cases it may be enlarged and palpable. The cut surface is often bloody and greasy and the lobular pattern is usually exaggerated The kidneys are sometimes tense and swollen, with scattered medullary congestion

The gastric and intestinal contents frequently contain altered blood, and the intestinal mucosa is peppered with petechial haemorrhages most prominent in the upper duodenum and stomach

Histological changes. The changes in the liver tissue are of diagnostic importance. They are essentially non-inflammatory although there may be a small degree of cellular infiltration of the parenchyma

[illegible]

lobule but is often most pronounced in the midzonal region; it is usually well developed in the central zone, but in the region of the central vein there are often a few less affected cells which have escaped the coagulative changes and have undergone fatty degeneration. The vessels of the lobule may be considerably congested; there are rarely haemorrhages.

days from the onset The pulse rate is high at first but drops rapidly so that a discrepancy between pulse and temperature develops Occasionally the temperature may rise after the onset without much corresponding change in pulse rate The increasing slowness of the pulse rate relative to the temperature (Faget's sign) is of diagnostic value

Peripheral congestion is pronounced giving the face a blotchy appearance Conjunctival injection and photophobia develop early Bleeding from the gums and nose may occur Headache, backache and limb pains are severe The patient is restless and considerably more prostrated than might be expected from the fever Gastrointestinal disturbances are the rule and appear early There is severe epigastric discomfort and tenderness, anorexia, nausea and vomiting The vomit contains excess bile and sometimes altered blood Watery bilious diarrhoea or melaena may develop

Jaundice becomes visible about the fourth day It is usually not pronounced and may be no more than an icteric tinge in the conjunctivae The yellow colour can sometimes be recognized after blanching the skin with pressure In some epidemics cases have been described in which jaundice was intense and developed rapidly, resembling the picture of fulminating infective hepatitis

Albumin appears in the urine on the first day and increases steadily in amount Tubular casts appear and the urinary volume falls to oliguric levels

With the fall of the temperature the patient feels better and the signs and symptoms subside The vomiting stops, the epigastric discomfort diminishes and recovery may now take place

In the more serious cases after a few hours to two days of remission the fever returns and the patient passes rapidly into a state of severe intoxication and prostration

The temperature rises rapidly but seldom reaches the level attained in the primary febrile period The pulse at first quickens a little but remains slow in proportion to the fever, and often continues to fall until by the tenth day it may be as slow as 40 beats per minute After usually not more than three or four days the temperature again falls In fatal cases the pulse rate frequently rises sharply towards the end at a time when the temperature is falling

Most of the signs present in the early febrile period become exaggerated Epigastric discomfort, nausea and vomiting become very severe Bleeding from the mucous membrane of the gut leads to vomiting of changed blood, sometimes in large amounts – the so-called black vomit Blood also appears in the stool

In the classical case, jaundice increases slightly In a few cases it may become considerable but it is usually much less evident than the name of the disease would suggest Bile appears in the urine

and discomfort may be severe. Some mild icterus may develop by the fourth day, fading rapidly in convalescence.

Protein appears in the urine on the first day and increases in amount until recovery. The urinary volume is reduced and there are usually tubular casts.

The whole syndrome lasts only a few days, after which the temperature falls to normal and recovery is rapid and complete.

THE CLASSICAL PICTURE

In previously unexposed subjects the disease is much more serious It develops in two main phases, separated by an interval of comparative calm

The first phase is very similar to that described above, but more severe

The onset is abrupt The temperature rises, frequently with rigor, to 102 to 104° F, and remains at about this level for one or two days, subsequently falling slowly to normal or near it about three or four

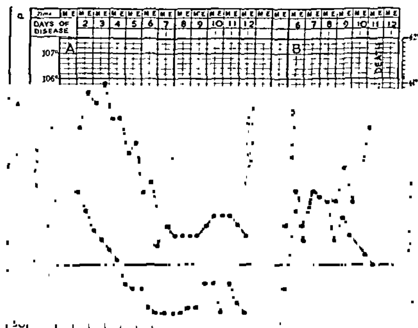


Fig 57 Temperature and pulse chart in Yellow Fever (After Faget)

A Case which recovered Note falling pulse and high temperature (Faget's sign)

B Fatal case Note the rising pulse and falling temperature – a bad prognostic sign

Clotting time is increased Prothrombin

... lymphocytosis and granulocytopenia with a shift to the left ... reduced The

changes in

... from vomiting, bleeding and diarrhoea in severe cases the chloride content of plasma is low In the more advanced stages there is often a notable reduction in blood sugar The blood urea nitrogen and non-protein nitrogen concentrations rise considerably especially in cases in which there is severe oliguria or anuria and uraemia The bilirubin content of the plasma rises and increases progressively as the jaundice develops The indirect, biphasic and, later, direct van den Bergh reactions are positive

The Urine The urinary volume is usually low from the beginning, especially when vomiting is severe The chloride content is also low Albumin is present from the onset

... haemorrhage into the urinary tract Bile is present in the late stages

The Vomit In the early days of the disease the vomit is watery or mucous and contains bile sometimes in considerable amounts Unaltered or swallowed blood from buccal or nasal bleeding may be present In the later stages the vomit contains brown or black altered blood – the so-called coffee grounds – arising from haemorrhages in the mucosa of the stomach

DIAGNOSIS

The clinical diagnosis of yellow fever in the isolated mild case is extremely difficult

The diagnosis in the severe case can be suspected in an endemic area on the grounds of sudden fever, conjunctival ... tion out of propor... jaundice appear ... the liver, Faget's

The clinical d... outbreak of yell... should be emplo...

Clinically, yellow fever may have to be distinguished from a variety

Fulminating cases may present with large liver and intense deepening jaundice.

Albuminuria increases. Oliguria sets in and renal failure with anuria, rising blood urea and acute uraemia may develop.

Petechial haemorrhages appear in the mucous membrane and sometimes under the skin Bleeding from the nose and lips may become more severe, and fresh blood may appear in the vomit.

In the late stages there is often intractable hiccup.

Death commonly occurs from vascular failure. It may be sudden or heralded by rapid fall of blood pressures, haemoconcentration and quickening pulse rate

The overall picture of the second febrile stage may be dominated by signs of hepatic, renal or vascular failure separately or together.

Throughout the disease the patient is usually conscious, anxious and restless. Delirium or coma occur only terminally and are not common In a few cases there may be late central nervous system signs including *meningismus, probably arising from vascular accidents*

Fulminating cases are occasionally seen, especially in epidemics, in which there is no period of remission and death occurs in a few days from the onset There is usually a very high fever with the signs of acute hepatic failure including deepening jaundice.

COURSE AND PROGNOSIS

The severe attack of yellow fever is over one way or another by the eleventh or twelfth day Death occurs most commonly between the fifth and eighth days The great majority of clinically mild cases recover completely in three or four days Prognosis must be guarded in [illegible] a high mortality amongst the severe cases which develop in non-immunes

LABORATORY FINDINGS

Blood cells The red cells are unchanged in the early stages Severe loss of blood by haemorrhage may be reflected in the later stages by some secondary anaemia If vascular failure develops, the anaemia may be temporarily masked by haemoconcentration affecting both red cell count and haemoglobin concentration.

the general symptoms tend to subside The liver becomes palpable and may be extremely tender Nausea, vomiting and anorexia may be severe at first The pulse slows to bradycardia and severe depression develops and persists throughout the jaundice, i e. sometimes for weeks. Once the jaundice has developed there should be little difficulty in distinguishing the ordinary case of infective hepatitis from yellow fever In fulminating cases the separation may be difficult In these cases, however, the temperature tends to be high and the pulse fast There may be a leucocytosis Jaundice appears in the first day or two and deepens rapidly. The liver is exquisitely tender but is usually not enlarged and may even be smaller than normal Final differentiation may have to depend on histological examination of the liver, the identification of the yellow fever virus or of a rising yellow fever antibody titre The histological picture in infective hepatitis is quite different from that of yellow fever The primary change is inflammatory with diffuse and focal mononuclear infiltration but extensive necrosis may appear in the severest cases.

Dengue The milder forms of yellow fever may be mistaken for dengue, especially when no rash develops, and can be separated only by identification of the yellow fever virus or an ascending titre of immune bodies in the blood In epidemics the absence of very severe or fatal cases of dengue is important. When there is glandular involvement in dengue there should be little difficulty

LABORATORY DIAGNOSIS

Specific Antibodies: The laboratory method most useful to the clinician is the identification of specific antibodies in the blood of the suspected case Antibodies capable of protecting mice from the neurotropic virus are present in measurable quantities by the fourth day of the human disease and increase rapidly in strength to reach full titre in about 10 days *In order to make a diagnosis it is necessary to demonstrate an increase in these antibodies over a period of days* Single examinations are not directly helpful, since immune bodies remain permanently in the blood after an attack, and a positive finding will merely indicate that an attack has at some [illegible]

and another about a week later, or, if possible, in convalescence Serum from the blood samples is tested for its protective powers against the neurotropic virus by the mouse protection test which can be carried out only in suitably equipped laboratories Mixtures of various dilutions of the unknown serum plus a fixed quantity of infected material containing the virus are injected intraperitoneally into white mice

of other somewhat similar conditions, which are enumerated below

Blackwater Fever The jaundice in this condition appears very early, often on the first day, and tends to deepen rapidly. The liver is commonly palpable and tender There is severe and probably progressive anaemia and haemoglobinuria or a history of it. The previous history of the patient in regard to malaria is important.

Malaria and Bilious Remittent Fever: Falciparum malaria may cause early and deepening jaundice, often associated with other signs of liver failure and vascular collapse. The liver enlarges and becomes tender. The spleen is enlarged There is usually severe anaemia and heavy parasitaemia In the course of the syndrome there is no period of remission, and Faget's sign is absent.

Relapsing Fever: High fever, albuminuria, jaundice and black vomit may occur in relapsing fever and be mistaken for yellow fever. Differentiation can sometimes be made only by identification of the spirochaete in the blood or in mice following inoculation of blood

Weil's Disease· The abrupt rise of temperature at the onset, the early conjunctivitis, the appearance of jaundice about the third day, the nausea and vomiting and sometimes haematemesis, are all suggestive of yellow fever However, about half the cases do not become jaundiced and in those that do the jaundice usually becomes intense, and the liver enlarges and becomes tender The initial fever persists for longer than in yellow fever The history of the case may be of some help, but diagnosis can only be satisfactorily made in the early stages by identification of the leptospira in the blood or in guinea pigs following intraperitoneal injection of the patient's blood, or urine after the tenth day After three weeks, examination of the plasma for agglutinins for [illegible]

[illegible]

former is extremely common in some parts of the tropics, including those regions in which yellow fever is endemic Confusion with the latter may occur in the early pre-icteric stages and in fulminating cases A history of exposure to a known case of hepatitis or to intravenous arsenical or serum therapy is often helpful Infective hepatitis has an incubation period of 3 to 5 weeks, syringe hepatitis of 6 weeks to 5 months. In most cases of infective hepatitis there is a pre-icteric febrile stage which may last a week or longer, in which the pulse is fast and the patient complains of malaise, anorexia, nausea and epigastric discomfort including tenderness over the liver region. Albumin may be present in small amounts in the urine, but does not increase in quantity [illegible] occa-

[illegible] xacer-

[illegible] days

Treatment is largely symptomatic Small frequent drinks containing glucose should be administered If vomiting makes this impossible glucose drip infusion should be given intravenously Isotonic glucose saline should be substituted if there is notable dehydration The appearance of shock calls for immediate infusion of plasma (For details see pp. 48, 49, 127)

A fluid intake/output balance must be kept All specimens of urine passed should be measured and examined, in order to keep check on the appearance of anuria

Procedures designed to lessen the liver damage, such as the administration of vitamin K, have provided equivocal results It is possible that in some cases the intravenous infusion of protein hydrolysates may be helpful

Antipyretics should not be used

PROPHYLAXIS

Entomological Control Urban yellow fever can be effectively controlled by eradication of the vector *Aedes aegypti* by destruction of breeding places and spray killing of adults Continuous control by such measures has largely terminated transmission of the urban disease Similar methods to those employed for malaria control have been used successfully in controlling rural yellow fever Jungle fever is not amenable to entomological control

Vaccination Protection of individuals and communities may be afforded by the use of vaccines prepared from the attenuated living virus

Antibodies demonstrable by the mouse protection test are present in the blood of most individuals 10 days after inoculation with the vaccine, they remain in the blood in undiminished strength for years It is considered that protection against the disease is assured in most vaccinated persons for six years after vaccination International quarantine regulations recognize this period in vaccinated persons, those who have had the disease are regarded as being permanently immune Non-immunes who have been exposed to infection in endemic areas are not admitted into non-endemic regions in which the vectors exist, except under surveillance until the expiry of the incubation period of the disease, which is reckoned as 10 days

Vaccines The original virus isolated in rhesus monkeys in West Africa was later found to produce encephalitis in white mice After serial passage through mice it was observed to lose its power of reproducing the disease in monkeys although it retained its effect on mice This altered virus, called 17D after its original laboratory number, was subsequently grown on chick embryo and is now used as the basis of American and British yellow fever vaccines A somewhat similar

previously prepared by intracerebral injection of minute quantities of sterile starch solution. The animals are left, with suitable controls injected with virus only, for a period of 4 to 6 days The control animals die If the serum contains active antibodies, some or all of the other mice will survive, and the titre of antibody is calculated accordingly The mixture of serially diluted serum and virus may be inoculated directly into the brain if desired. If the serum sample taken at the beginning of the illness does not contain antibodies and the final sample does, or if there is a significant increase in titre in the second specimen compared with the first, the diagnosis is established.

The mouse protection test is also valuable for surveying endemic areas, since individuals once infected appear to carry antibodies for life The immune content of sera taken from random samples of the population will thus indicate whether the disease has occurred in the district The immune content of serial samples from young children taken over an interval of a year or more will indicate further whether the disease is still active in the locality The overlap of immunity with that induced by other viruses must be taken into account in making these assessments

Identification of the Virus Blood taken within the first 72 hours of the disease contains the virus and can be used to infect rhesus monkeys The subsequent identification of the virus is a highly technical procedure which can be carried out only by specially equipped laboratories Unless these are available attempts to passage the virus should not be made, as they are decidedly dangerous in inexpert hands

Histological Examination of the Liver Coagulative degeneration of hepatic cells, and possibly nuclear inclusions can be demonstrated in early cases in sections of liver tissues fixed in formalin and stained with eosin and haematoxylin. In fulminating or late cases there may be so much tissue destruction that identification is difficult On the whole, however, a firm diagnosis can usually be made from histological material if the observer is sufficiently experienced

In endemic areas examination of liver tissue should be carried out as a routine in all fatal febrile illnesses of short duration. The tissue samples may be removed from the cadaver by an instrument called a viscerotome, they are fixed in formalin, and examined subsequently

TREATMENT

There is no specific treatment for yellow fever Convalescent serum, penicillin and sulphonamides are ineffective

The patient must be carefully nursed in bed He should be kept as quiet as possible and not moved unless absolutely necessary. He must be nursed under a mosquito net at any rate for the first four days after the onset.

An attack induces immunity against the homologous strain of the virus lasting about a year and affording protection against other strains for a variable period of months

The Vector The females of numerous species of Aedes mosquitoes are capable of transmitting the disease By far the commonest natural vector is *Aedes aegypti*

Transmission The virus is present in the blood of the human patient for as long as three days after the onset and possibly for a short time before The mosquito becomes infective 8-12 days after ingesting blood containing the virus (the extrinsic incubation period) It remains infective for the rest of its life It injects the virus into the host during biting

Infection may be transmitted artificially by injection of infected blood

Transmission depends on the presence of the vector, suitable infective individuals, and non-immune hosts

Breeding and activity of the vector are maximal in hot moist conditions, and minimal in the cold The disease is therefore often seasonal in its incidence, occurring in the wet season in the tropics or summer and autumn in the subtropics

Man is the usual reservoir of the infection, certain macacus monkeys which can be infected by laboratory strains may also act as such

Non-immunes of any race and age and of either sex are susceptible

Transmission may be kept up by the reinfection of local inhabitants who have lost or are losing immunity acquired in previous attacks, or by infection of visiting non-immunes

When the latter are numerous or when the local community has been free from the disease for over a year, explosive epidemics appear, which burn themselves out after involving the majority of susceptible individuals

PATHOLOGY

There is no information available Changes in the blood are described in the next section

CLINICAL PICTURE

The clinical picture varies widely from individual to individual in the same outbreak and from epidemic to epidemic, this is also true of cases artificially infected under laboratory conditions The disease lasts anything from 1 to 10 days

The incubation period varies from 4 to 13 days, with a mean range of about 5 to 9 days from the time of infection There are often prodromal symptoms including malaise, headache and mild shivering, which come on two or three days before the onset

vaccine has been developed by the French, made from a virus which is passaged by serial intracerebral inoculation of mice

The 17D virus is prepared as the attenuated dried living virus which is suspended in saline immediately prior to injection subcutaneously, and which must be stored at low temperatures The French vaccine is simply the dried infected mouse brain and is more stable and resistant to heat, it is suspended before use in gum arabic solution and administered by scarification in the same way – and often at the same time – as smallpox vaccine. The 17D virus has recently been adapted for administration by scarification

There is no local reaction to the injection of 17D vaccine and no general reaction beyond occasional headache and malaise. Modern vaccine is supplied in dried powder form after suspension in either saline or albumin during its manufacture; it was formerly diluted with human serum which on occasion became contaminated with a virus causing hepatitis

The neurotropic French vaccine gives a higher immune titre in the mouse protection test than the 17D vaccine, but there is no evidence that this higher titre represents an increase in the degree of protection against the disease in man The French vaccine has been reported to *give rise from time to time to encephalitis. It is not commonly used in* children under three years of age.

DENGUE

DEFINITION

Breakbone fever. An acute non-fatal virus infection transmitted by Aedes mosquitoes

GEOGRAPHICAL DISTRIBUTION

Dengue occurs in most of the subtropics and tropics, especially in coastal areas It appears in southern North America, South America including Brazil, the West Indies, the Mediterranean seaboard, Egypt and the Middle East, north, central and South Africa, Greece, southern Russia and Turkey, India, China, many Pacific Islands including the Philippines, the Solomon Islands and New Hebrides and Northern Australia

AETIOLOGY

Causal agent Dengue is caused by a filterable virus There are at *least three antigenically overlapping strains so far identified by passage* in mice.

subside This is followed by a secondary febrile period which lasts two or three days, ending by lysis The temperature rises suddenly, usually to a somewhat lower level than in the primary fever but occasionally exceeding it

The primary and secondary febrile phases separated by an afebrile remission constitute the classical saddleback fever Experience has shown that this is no more common in dengue than the simple continuous remittent fever

With the reappearance of fever the pulse rate rises for a short time, then falls to the level obtaining at the end of the initial febrile stage The signs and symptoms return with the fever, but are usually not so severe as in the first stage

The Rash The true dengue rash seldom develops before the fourth or fifth day In cases in which the fever is saddlebacked, the rash nearly always appears during the second febrile phase, commonly within a few hours of the reappearance of the fever

Many cases never show a rash In others it may be fleeting or become a dominant feature In some districts the majority of cases develop a rash, in others the minority The rash may be characteristic of a particular epidemic and absent in others

It is morbilliform, fades easily on pressure, and is very bright red, contrasting with the bluish tinge of measles In very severe cases, or in certain epidemics it may be complicated by petechial haemorrhages

It appears first as a rule on the dorsal surface of the hands and sometimes the feet, it spreads rapidly to the arms and legs and often includes the trunk, it sometimes involves the face It comes up very rapidly and begins to fade as the temperature subsides Fine desquamation associated with some brown pigmentation usually occurs

The eruption is intensely itchy, especially during desquamation, and scratching may lead to secondary infection The pruritus may be the over-riding concern of the already depressed sufferer, leading to insomnia and deeper depression

The blood cells There are no specific changes in the erythrocytes, or the erythrocyte sedimentation rate

Leucopenia develops immediately, sometimes before the fever, and rapidly becomes severe, the white cell count reaching 2000 to 3000 cells per cu mm by the fourth to sixth day, independent of the fever Recovery of the cell count is slow, and takes place a week or more after the fever has subsided

The leucopenia results from a reduction in all forms of leucocytes most pronounced in the granulocytes The proportion of lymphocytes present is high, of the order of 60 to 65 per cent The Arneth counts show a decided shift to the left As the white count returns to normal the increase first appears in the granulocytes

The onset is abrupt The patient can often recall the time almost to the hour The temperature rises sharply to 102° to 105° F, frequently with rigor.

Many of the other signs and symptoms begin equally suddenly.

The most impressive symptoms as a rule are headache and intense agonizing pains in the joints, long bones and back, which may be so severe as to prevent sleep

The headache is sometimes diffuse, sometimes concentrated in the post- and supra-orbital regions. The eyeball and muscles about the eye become tender to touch, and movements of the eyes are painful.

The bodily pains are shooting in character and accompanied by considerable soreness on pressure over muscles and tendons The joint pains are centred in the muscle insertions and the joints proper are not normally involved.

The appetite is lost completely. Nausea is common and vomiting may be frequent and severe There is usually epigastric discomfort and tenderness

A blotchy congestion of the peripheral circulation, particularly notable in the face, develops early producing an effect which is sometimes referred to erroneously as the primary rash.

Epistaxis is common

Photophobia is often pronounced and may be accompanied by puffiness of the eyelids, severe conjunctival injection and excessive lachrymation

There may be a slight cough in the early stages, but respiratory symptoms are minimal and the nasopharynx is not involved.

The patient is restless and anxious; there is acute depression and often unreasonable fear regarding the outcome of the illness Insomnia is the rule, sleep occurring in short spells often broken by disturbing dreams

The pulse is fast at the onset It sometimes falls in time with the temperature, sometimes so rapidly as to simulate Faget's sign in yellow fever It may reach a rate of 50 or 60 beats per minute within the first four or five days, persisting at that level throughout the course of the illness, and often for several days into convalescence

The fever varies from patient to patient It is initially high and remittent and tends to be continuous, falling to normal after the first three or four days, usually by crisis associated with sweating and often diarrhoea

During the fever there may be slight albuminuria but this is not a constant feature

In many cases the temperature now remains normal and the patient passes into convalescence. In others there is a remission lasting a few hours to two days, during which the symptoms almost completely

SANDFLY FEVER

DEFINITION

Sandfly fever Papataci fever Three-day fever. An acute infectious non-fatal virus disease transmitted by the sandfly *Phlebotomus papatasi*

GEOGRAPHICAL DISTRIBUTION

The distribution depends on that of the fly The disease is common in many parts of the tropics and subtropics, appearing mainly in the hot dry weather It occurs in Portugal, the Balkans, Italy, the Aegean Islands, most of the Mediterranean littoral, Egypt and the Middle East, east and north Africa, India, Burma, China and parts of South America as far south as northern Argentina

It has been reported in communities living 5000 feet above sea level

AETIOLOGY

The causal agent is a very small filterable virus which exists in several closely allied antigenic strains Monkeys have been infected intracerebrally but otherwise the organism has not so far been passaged to animals

During the disease the virus is present in the patient's blood for one to two days before the onset and for about a day afterwards

The reservoir of infection is man.

The Vector Females of several species of phlebotomus flies or sandflies can transmit the infection The commonest is *Phlebotomus papatasi* These insects are most active and voracious at night, resting during the day in cool shady dry places such as cracks in stonework They never fly far from their breeding grounds The limit of flight is usually 50 to 100 yards

Transmission The fly becomes infective 6 to 8 days after ingesting human blood in which the virus is circulating It remains infective for life It is believed to pass the infection to its offspring

The disease is transmitted by the bite of the infected fly It can be passed experimentally from man to man by injection of infective blood

Epidemiology The disease is highly seasonal in its incidence, occurring in most districts in the late spring and sometimes becoming epidemic in the summer It disappears in the autumn and winter

No race is immune Both sexes are freely attacked at all ages

All non-immunes are highly susceptible and will almost certainly become infected on entering an endemic area at the right time In an

Lymph glands. Moderate enlargement of lymph glands, which may be general and symmetrical or confined to certain groups, is a striking feature of the disease in some districts and in certain outbreaks. It is not, however, a constant finding.

The glands are palpable, only slightly tender, and remain discrete. Enlargement starts early and is evident by the second day. Subsidence in convalescence is slow. Suppuration does not occur without secondary sepsis.

PROGNOSIS

Dengue is a non-fatal disease. The most serious complication is profound depression which may continue for several weeks after the subsidence of the active disease and is often aggravated by the intense pruritus. Despite this depression there is little evidence to support the firmly held view that suicide is common after the disease. Complete recovery is the rule, although convalescence may be very slow.

DIAGNOSIS

During a known outbreak the diagnosis is usually easy, particularly if certain features are present, including the very abrupt onset, severe headache and bone pains, the saddleback fever, bradycardia, the rash, and rapidly developing leucopenia and shift of the Arneth count to the left.

The individual case may present considerable difficulty and confusion may arise with almost any acute febrile illness, especially measles, malaria, yellow fever, phlebotomus and other similar fevers, and influenza. In measles distinguishing features are the early coryza, Koplik spots and the widespread rash first appearing on the face. Yellow fever may be distinguished by the increasing albuminuria, the appearance of jaundice and Faget's sign, the absence of a rash or marked changes in leucocytes, and by immunological techniques. It *is often impossible to separate phlebotomus fever from atypical dengue,* unless there is good evidence regarding the vector.

Influenza also causes great difficulty at times, but can usually be distinguished by the acute upper respiratory involvement and the absence of rash, changes in the leucocytes or lymph glands.

There is no certain laboratory method of diagnosing dengue.

TREATMENT

Treatment is entirely symptomatic. Severe pain and restlessness may require aspirin, codein or morphia. Barbiturates are needed for the insomnia.

Calamine lotion or antihistaminics may relieve the pruritis.

cells are reduced much less in proportion, producing a relative lymphocytosis The blood changes take a week or more to recover after the illness There is no rash and no glandular involvement The erythrocyte sedimentation rate is seldom affected

PROGNOSIS

The disease is non-fatal in spite of the fact that it is very severe while it lasts The depression is relieved only slowly and convalescence may be a matter of weeks

DIAGNOSIS

There is no laboratory method of making a certain diagnosis [illegible] but [illegible]

TREATMENT

Treatment is entirely symptomatic

RIFT VALLEY FEVER

DEFINITION

An enzootic of sheep occurring in Kenya, sometimes transmitted to man

GEOGRAPHICAL DISTRIBUTION

The disease has been recognized in man in the Rift Valley,, Kenya and in numerous laboratory accidents and experimental infections It is probably widespread Surveys have shown that antibodies appear in man in the Anglo-Egyptian Sudan, French Sudan, parts of French Equatorial Africa and Uganda, but not in West Africa

AETIOLOGY

The disease is caused by a filterable virus which occurs naturally in sheep and possibly also in goats and cattle

The virus has been successfully passaged to monkeys, rabbits and mice in which acute hepatic necrosis develops A fixed neurotropic virus has been established in the latter Protective antibodies are

epidemic the natives of the area are usually unaffected, indicating the presence of considerable resistance to infection, probably acquired by repeated past infection. Evidence of immunity has recently been obtained by study of the laboratory transmitted disease in humans. It is strongly developed for the homologous strain, but appears to be of short duration Fresh attacks can develop within a few months of an infection There is some cross-immunity between various strains of phlebotomus virus but none with dengue.

PATHOLOGY

Phlebotomus fever is non-fatal Nothing is known of its pathological effects on the tissues The changes in leucocytes are mentioned below.

CLINICAL PICTURE

An attack of phlebotomus fever closely resembles one of dengue without the rash, saddleback fever or glandular involvement. The whole affair seldom lasts more than three or four days

The incubation period varies from 3 to 7 days

The onset is very sudden. There is a rapid rise of temperature to 103° to 105° F, often associated with rigor Thereafter the temperature remains elevated for one to three days, rarely longer. The fever is remittent and ends by crisis accompanied by intense sweating and sometimes epistaxis In a few cases there may be a short remission followed by a few further hours of fever, the temperature chart thus resembling the saddleback fever of dengue.

The signs and symptoms appear as abruptly as the fever, usually without any marked prodromata. The peripheral circulation is congested This is especially marked on the face. The conjunctivae are injected, photophobia and lachrymation are common. There is very severe headache and pain especially at the back of the orbit. Long bone, joint pains and backache are very troublesome and may be severe enough to cause insomnia The patient is deeply depressed and feels very ill and worried about his condition. Anorexia may be complete Nausea is common and there may be some vomiting The pharynx is injected and sore and there is usually some mild bronchitic involvement which results in an unproductive cough; there may be a few scattered râles The pulse is often slow in relation to the fever, it may be very fast Leucopenia develops immediately after the onset The total count may fall as low as 3000 cells per cu mm There is an absolute reduction in polymorphs, with a relative increase in young cells, causing a considerable shift to the left The lymphocytes and other

confirmation and distinction from influenza, dengue and phlebotomus fever, unless the latter two diseases can be excluded on epidemiological grounds

Rift Valley fever virus contained in the blood at the height of the fever will kill mice in about 4 days after intraperitoneal injection Blood from the other infections mentioned has no effect

Treatment is symptomatic

produced during infection in man (after a few days) and other animals and can be demonstrated by intraperitoneal assay in mice. The virus has been found in certain mosquitoes in the forests of Uganda In monkeys there is some cross immunity with yellow fever and *vice versa.*

In lambs the disease is often fatal. Adult sheep are more resistant. Cases of suspected infection commonly occur amongst shepherds during epizootics.

The mode of transmission is unknown, but it is believed that certain mosquitoes may be concerned Transmission in the laboratory probably occurs through abrasions on the skin or via the nasopharynx.

The virus is present in the blood of human cases in the early stages of the clinical reaction, and for some time afterwards.

PATHOLOGY

[illegible]

and mesenteric lymph glands are enlarged and may be haemorrhagic. Haemorrhagic enteritis with bloody stools is sometimes seen. The only fatality in man occurred following pulmonary embolism six weeks after the onset of an accidental laboratory transmitted infection

CLINICAL PICTURE

The onset is sudden and occurs within a few days of blood inoculation or after a period of 5 to 6 days in the natural infection

The patient complains of malaise, sore throat, sometimes epistaxis, body pains especially in the joints, and usually abdominal fullness, discomfort and even tenderness, particularly in the upper right quadrant There may be nausea and vomiting has been reported Photophobia is common, the conjunctivae may be injected Fever is usually mild and of short duration It tends to subside by the third or fourth day; a short secondary rise may occur

A moderate leucopenia characterized by granulocytopenia develops which may persist into convalescence

There is often tenderness over the liver region, but signs of hepatic dysfunction are absent and the blood bilirubin is not raised Bile does not appear in the urine

DIAGNOSIS AND TREATMENT

Clinical diagnosis may be possible in those in contact with infected animals during an epizootic Laboratory methods are essential for

the lungs, where they lodge The vermicules penetrate into the alveoli, are expelled via the bronchioles, bronchi and trachea, are swallowed and then pass through the stomach to the small bowel, where they become adult males and females

The migration of large numbers of larvae at one time may cause a severe verminous pneumonitis There is a cough, with blood-stained sputum in which larvae may be found on microscopical examination In certain susceptible persons, under these conditions, there may be generalized allergic manifestations, with an eosinophilia When the number of migrating larvae is small their passage usually escapes notice

A few adult worms in the small intestine do not usually give rise to any symptoms A worm or worms may be passed in the stools When a worm wanders from its normal site of election into the stomach it may be vomited Sometimes a worm ascends the oesophagus and passes through the nasopharynx to emerge from a nostril It is by such events that the patient is made aware of the infestation

Numerous worms, and they may number as many as two hundred, in the small bowel cause abdominal discomfort and distension A small child with a heavy ascaris infestation will have a protruding belly; intestinal obstruction, perforation, or volvulus may be a result of the infection Occasionally worms ascend the common bile duct or pancreatic duct and cause obstruction of them, or may rupture them

DIAGNOSIS

If mature female worms are present ova will be found in the stools on microscopical examination These ova may be infertile if female worms alone are present, or fertile if both sexes are represented

Eosinophilia, except when there is an allergic reaction to the worms, is unusual

TREATMENT

Santonin has been used for many years in the past but it causes troublesome side-effects and is little used today

As those with an ascaris infestation usually harbour other helminth parasites, particularly hookworms, a mixture of oil of chenopodium and of tetrachlorethylene, which are effective against both parasites, is commonly employed in tropical practice

After a light diet for twenty-four hours a saline purge is given For an adult a few hours later 1 cc Ol chenopodii and 2 cc tetrachlorethylene are given in half an ounce of liquid paraffin This is followed by a stiff saline purge two hours later to sweep out the affected worms

XLIII

WORM INFECTIONS, MISCELLANEOUS

ASCARIASIS

DEFINITION

ASCARIASIS is the condition of infestation with the large round-worn, *Ascaris lumbricoides*. Light infestations rarely cause clinical signs; heavy infestations may result in symptoms and signs due to the mechanical effects of the presence of the worms.

GEOGRAPHICAL DISTRIBUTION

This parasite occurs ubiquitously irrespective of climate; it is most prevalent where cleanliness and sanitation are defective or absent

AETIOLOGY AND CLINICAL PICTURE

The worms are large, ivory-white and cylindrical with pointed ends They are of two sexes, the males, which have coiled tails, measure about seven, and the females about nine, inches in length The adults inhabit the lumen of the small bowel, where they are unattached and move freely They possess an alimentary tract and gain their nutriment from the intestinal contents The females, whether impregnated or not, extrude numerous eggs which are passed in the stools of the patient In the fertilized eggs, after passage to the exterior, there develops a vermicule The egg is then infective if swallowed The eggs are extra-

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FIG 58 *Ascaris lumbricoides*, male and female Scale in cms [From E Noble Chamberlain *A Textbook of Medicine* John Wright & Sons Ltd, Bristol, 1951]

explained by these facts Infestation with numerous worms is the result of gross faecal pollution of food or drink

On swallowing eggs containing vermicules the latter emerge, bore into the wall of the small intestine, and are carried in the circulation to

the bowel The adult worms live unattached and free in the lumen of the lower small and the large intestine They have an alimentary tract and obtain their nutriment from the intestinal contents The partu- [illegible]

ferred to towels and other linen A vermicule develops in each fertile egg, and these embryonated eggs are infective if swallowed On being swallowed the vermicules develop into adult male and female worms within the bowel without any migration during their growth

The worms within the intestine rarely cause symptoms, though it is said their presence in the vermiform appendix may precipitate an attack of appendicitis The migration of the parturient female worms through the anus particularly at night to the surrounding skin causes severe itching, which may become intolerable and seriously interfere with sleep The consequent scratching may result in a septic dermatitis In the process of scratching the fingers and finger nails become contaminated with embryonated eggs, which can thus readily be conveyed to the mouth This is especially the case with children, who tend thus to reinfect themselves to an increasing degree Cross infection by contamination of linen and towels readily occurs, and when one member of a household becomes infected with threadworms sooner or later the remainder are likely to acquire the infection It is therefore advisable to ensure that no more than a single person of a family is infected before undertaking only his treatment

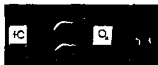


FIG 59 *Enterobius vermicularis* Actual size
[From E Noble Chamberlain *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

DIAGNOSIS

In cases of heavy infestation the patient may notice female worms on his finger tips after scratching the perianal region

Usually in suspected cases of infestation a search is made for the eggs Occasionally a worm may be seen in the stools, but the eggs are not passed in the stools and it is a waste of time examining these for them The eggs must be sought for on the perianal skin A scraping may be made with a knife blade, preferably on rising from the night's rest Better, a swab consisting of a small piece of Cellophane on the end of a wire, glass-rod or stick can be rolled over the area The eggs adhere to the Cellophane, which is opened out, moistened, and examined microscopically for them under a cover-slip

and to expel the drugs. It is important for both purposes and should never be omitted, if the drugs are left they may be absorbed and cause grave toxicity; if the worms are left they may recover and re-establish themselves.

Hexylresorcinol, in a dose of 1 gm for an adult and half this dosage for a child of 10 years, is a safe and effective anthelmintic for ascaris, particularly in children. Caution should be exercised when treating children with large loads of ascarids; if all the worms are affected simultaneously a tangled mass of them may result in intestinal obstruction. Repeated dosage with smaller amounts of drug, and the removal of a few worms at a time, is wiser under these circumstances

Piperazine salts (the citrate, adipate or phosphate) when given as a single dose are claimed to be effective ascaricides. The dose is 4 gm; this should be followed next day by a saline purge to evacuate the affected worms Prepared in the form of a syrup the drug is acceptable to children, and given in a single dose does not cause toxicity.

Bephenium hydroxynaphthoate (Alcopar) which is stated to be an effective anthelmintic against hookworms is also claimed to be as effective against *Ascaris* The dose for adults is a single one of 5 gm; that for infants under two years of age is half this. When there is diarrhoea treatment should be continued for three days. Neither fasting nor *purging is necessary, and the treatment is devoid of toxicity. If the* initial results are confirmed this drug should prove a valuable means of eradication of *Ascaris* and hookworm infection

ENTEROBIASIS

DEFINITION

Threadworm or pinworm infestation is due to the presence in the intestine of the small nematode *Enterobius vermicularis* The emergence of the gravid female worms from the anus on to the surrounding skin causes irritation Scratching may result in a severe dermatitis

GEOGRAPHICAL DISTRIBUTION

Worldwide and uninfluenced by climate

AETIOLOGY AND CLINICAL PICTURE

Enterobius vermicularis is a strict human parasite The worms are small, white and thread-like; the sexes are distinct; the males, which have coiled tails, measure about 5 mm, and the females 10 mm in length. The insignificant males are rarely seen as they perish within



FIG 60 Skin reactions in strongyloidiasis

coralis, especially common in parts of China, Siam, South America and Africa, and other areas which are suitable for development of the worm The life cycle of the worm varies according to the environmental

TREATMENT

First, if possible, the cycle of self-reinfection must be controlled or broken This is attempted by scrupulous cleanliness, the wearing of

months

The older treatments consisted of smearing the perinaeum with a mercurial ointment and giving enemata of such astringent fluids as infusion of quassia The ointment was of doubtful value, and the enemata of quassia were in no way superior to, and probably less effective than, enemata of soap and water or of brine. The enemata are beneficial mechanically in removing the worms from the lower large bowel, and they afford much relief from the itching caused by the spontaneous emergence of the female worms They may profitably be repeated on alternate mornings for a week or two, each after an *overnight dose of calomel*

Hexylresorcinol in doses of 1 gm daily for an adult, and half this for a child of 10 years, over a period of a week is said to kill threadworms, it is claimed to be safe even when given by the school nurse to children attending daily.

Phenothiazine, an anthelmintic much used in veterinary practice, is very effec

5 days is

daily for

severe haemolytic anaemia and toxic hepatitis are said to have followed its use in children, and as a result it has been regarded as too dangerous for pediatric practice

Piperazine salts (the citrate, adipate or phosphate) are effectively anthelmintic to the human thread worms, and now supplant the drugs previously used Given in the form of a syrup (Antepar) daily for a week to children the cure-rate is high The daily dosage for such a course is 300 mgm of the citrate for each year of age up to a maximum of 1.8 gm.

With all anthelmintics, possibly with the exception of hexylresorcinol, fatalities from time to time have occurred None, therefore, should be given lightly and without careful control.

STRONGYLOIDIASIS

DEFINITION. LIFE CYCLE

A widely spread condition due to infection with *Strongyloides ster-*

DIAGNOSIS

The motile larvae closely resembling those of the hookworm can be seen in low power preparations of faeces Ova are rarely passed, the ovum usually contains a fully developed larva which, unlike the hookworm, hatches before the faeces are expelled

Larvae are not usually found in skin eruptions

TREATMENT

Dithiazanine iodide (Telmid) appears to be the most satisfactory drug at present available The dosage regime for an adult is 200 mgm thrice daily for one up to three weeks There are no serious toxic effects

Medicinal gentian violet is sometimes used in adult doses of 50 mgm thrice daily for 2 to 3 weeks

LARVA MIGRANS

Cutaneous (creeping eruptions)

The larvae of certain nematodes unnatural to man, and occasionally the larvae of *A duodenale* and *N americanus* may cause cutaneous lesions, called creeping eruptions, which result from their presence in the immediately subepithelial skin layers Common causes of creeping eruptions are *Ancylostoma braziliense* and *Ancylostoma caninum*, the hookworms of cats and dogs

A minute papule may appear at the site of entry of the larva From here the larva moves irregularly about, forming a serpiginous tunnel between the corium and the stratum granulosum of the epithelium It may wander very slowly in this way for months and will not develop further while it remains in the unadapted host The lesion in the proximity of the wandering larva is at first erythematous, then raised above the skin surface and finally vesicular There is local infiltration with eosinophils and lymphocytes The active lesion is commonly surrounded by an arteriolar flare



Fig 61 Creeping eruption of foot

It occurs most commonly in the feet, hands and buttocks Serpiginous tunnels are burrowed by the larvae in the superficial skin layers of the skin A slightly raised erythematous vesicular eruption follows, accompanied by intense pruritus The lesions first appear as erythematous itchy papules 2 to 3 days after exposure and may last several weeks. They advance slowly As the larvae advance the lesions heal

circumstances. The basic cycle involves a free-living adult stage in warm moist faecal soil. Rhabditiform larvae are passed in human faeces and after three moults develop in the soil into free-living adults This cycle may be repeated indefinitely in the right conditions When conditions are bad fine delicate filariform larvae are formed. These pierce the human skin, reach the right side of the heart and escape through the pulmonary vessels into the alveoli. A few mature in the bronchi but the majority pass over the trachea to reach the small intestine. The males are passed in the faeces The fertilized females penetrate into the mucosa, where they lay dozens of eggs each day The eggs hatch in the mucosa *and the rhabditiform larvae escape into the lumen and thence to the stool* So long as the environment is suitable, the free-living cycle is repeated but sooner or later filariform infective larvae are again formed Sometimes filariform larvae are formed during the passage down the intestine and penetrate either the mucosa or the skin near the anus and repeat the tissue life-cycle; *this process is called auto-infection.*

In a given individual infection may persist for years.

CLINICAL PICTURE

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The most pronounced lesions occur in the skin, either as a result of local penetration or sensitivity reactions. An eruption, characterized by

hours, but *the manifestations as a whole may continue for some days* at a time, with long quiescent intervals between attacks Oedema and itching of the finger tips has been recorded. Areas of violently itchy urticaria, oedema and erythema, especially around the anal region, are also frequently attributed to strongyloid infection. It has been suggested that these arise from penetration of filariform larvae passed in the faeces, or from sensitivity reactions set up by them.

Lesions of deep tissue classified as visceral larva migrans have been reported *in autoinfectious with S stercoralis.* *(See p 489)* *Very heavy* auto-infection through the gut wall has recently been reported. Such infections may be fatal

of infection, and upon the organ affected General reactions include considerable eosinophilia

Rarely, larvae from *A braziliense* or *A caninum*, which have escaped from the skin into the circulation may cause similar lesions; these have also been reported in auto-infections with *Strongyloides stercoralis*.

GNATHOSTOMA SPINIGERUM

In many parts of the East, including India, Thailand and China, infections with this nematode have now been reported Infection follows the ingestion of raw fish flesh containing the encysted third [illegible]

variable size It may remain intermittently in one area for days or weeks or wander from one region to another It is usually itchy but painless, occasionally accompanied by severe boring pain It is firm and non-pitting and suppuration is rare Histologically there is intense inflammatory eosinophilic infiltration and the worm may sometimes be visible Occasionally it may be seen through the skin and can then be removed The worm has been removed from the *cervix uteri* in a case of leucorrhoea

The swelling is caused by the migration of the immature adult (about 6 mm by 0 8 mm) There is a high eosinophilia and various other systemic signs have been reported in individual cases, including paroxysmal coughing, haematuria and spontaneous pneumothorax

Diagnosis is made by finding the adult or by the use of specific antigens for skin reactions

Removal of the worm usually leads to cure since there is rarely more than one worm present

No chemotherapy has proved fully successful although relief has been obtained with the usual doses of hetrazan

The reservoir animals are dogs and cats The adults live in the stomach Eggs are passed in the faeces, hatch in water, and the larvae are ingested by *Cyclops* Fish eat the cyclops and the third-stage larva encysts in their muscles The infection of man thus occurs only in areas where raw fish is regularly consumed

WHIPWORM

Trichuris trichiura is a common nematode parasite of man It is world-wide in its distribution and is especially prevalent in the tropics The adult worms are of two sexes, they measure from 30 to 50 mm in length,

behind them, becoming dried and often crusted. Secondary infection from scratching is common

More transient lesions occur occasionally in aberrant infections with filariform larvae of *Strongyloides stercoralis*

Creeping eruptions somewhat similar to those due to aberrant round worm larvae may arise from cutaneous infection with the larvae of certain flies, for instance from infection with the larva of the horse bot fly (*Gasterophilus* spp), each lesion containing a single minute larva, which has hatched from eggs deposited on the hairs, usually of the limbs The much larger larva of the cattle warble fly *Hypoderma bovis* may give rise to similar lesions

Creeping eruption may be dealt with by local cauterization, by spraying the infected region with ethyl chloride or by the application of carbon dioxide snow or ethyl acetate Hetrazan has been used successfully in some cases due to helminths.

Visceral larva migrans

The importance of visceral larva migrans has only recently been discovered The lesions are produced by nematode larvae which gain access to the viscera of unadapted hosts, occasionally under unsuitable conditions they may be produced by larvae of nematodes in the natural host

In man the commonest lesions result from infection with the dog and cat ascarids *Toxocara canis* or *T cati*

[illegible]

development takes place but the larvae remain alive for months Single or multiple, even miliary, lesions may occur in this way, the number depending upon the number of eggs swallowed and hatched In infec-

[illegible]

Histological examination reveals a reaction not unlike an early tubercle, with an outer ring of lymphocytes and polymorphs, within which are layers of histiocytes and epithelioid cells which may be palisaded or form atypical giant cells. The granuloma is eventually walled off by concentric fibrosis In recently formed lesions the living larva lies near the centre and can be mechanically expressed It may ultimately become necrotic or calcified

Clinical signs depend on the number of lesions, i e upon the intensity

and mount up the bile capillaries where they finally lodge and mature The number of adult worms in a case of heavy infestation is very large

The presence of the worms in the biliary canals causes trauma and a local inflammatory reaction, after a time there appear crypt-like dilatations of the canals in which lie a number of worms There is a localized hyperplasia of the biliary epithelium with marked peri-

fibrosis, with consequent distortion of the lobular pattern The changes in the liver ultimately depend on the number of worms and the duration of the infection Light infections produce only minor effects Heavy infections lead to hepatic engorgement and enlargement, fatty parenchymal changes and finally cirrhosis The syndrome of portal hypertension associated with splenomegaly may develop, especially in alcoholic individuals Carcinoma of the liver or pancreas may occur

Pathological changes leading to fibrosis and sclerosis of the ducts may be initiated in the pancreas as a result of invasion by adults

'Toxic' effects of the infection include emaciation and cachexia especially in children Eosinophilia varies from 10 to 40 per cent

CLINICAL PICTURE

The symptoms are proportional to the degree of infection In light infections they are negligible, in heavy infections they are those of a chronic catarrhal cholangitis, with enlargement of the liver, some icterus, and wasting Systemic manifestations, such as tachycardia, vertigo, tremors, cramps, lassitude and mental depression, sometimes occur These are thought to be a result of impaired liver function due to a long continued heavy infestation

Diagnosis depends on the discovery of the eggs in the faeces or in the fluid aspirated from the duodenum

Skin tests, using antigens made from adults, are successfully used in China After injections 0 1 of the antigen intradermally a large wheal surrounded by flare develops within twenty minutes Differentation from other fluke infections may be made from skin tests using serial dilution of specific antigens

TREATMENT

There is no satisfactory specific treatment for clonorchiasis A course of sodium antimonyl tartrate, given intravenously has been stated to reduce the number of worms A similar claim has been made for gentian violet given orally Chloroquine has been used with some success (p 495).

the anterior part of the worms is slender and filiform and the posterior two-fifths is bulky and fleshy. The worms attach themselves by their heads to the mucosa, chiefly of the caecum and upper large bowel. The female worms discharge characteristic barrel-shaped bile-stained ova, which have a plug at each end

Infection results from swallowing eggs which have become embryonated some two weeks after being passed to the exterior in the stools The embryos emerge, attach themselves to the bowel wall, and grow into adult worms The presence of the latter causes no symptoms or gross pathology The diagnosis of their presence is made on finding the eggs in the stools

Dithiazanine iodide (Telmid) is stated to be anthelmintic to most of the nematodes which may infest the intestinal canal of man. In particular it is said to be effective against *Strongyloides stercoralis* and *Trichuris trichiura*, and also to act on the roundworm *Ascaris*, the threadworms and the hookworms to a lesser extent It is non-toxic and the dosage is 200 mgm thrice daily for 5 days given before the main meals.

FLUKES, HEPATIC

CLONORCHIS SINENSIS

Clonorchiasis is the name given to a state of infection of the bile passages with the trematode parasite *Clonorchis sinensis*

GEOGRAPHICAL DISTRIBUTION

The infection occurs only in the Far East, in some parts of which it is very prevalent. It is endemic throughout most of China and in Indo-China, Formosa, Korea and Japan.

AETIOLOGY

Clonorchis sinensis has been recovered from the livers of man, of the dog, of the cat, and of a number of other animals The adult flukes [illegible]

coming metacercariae. Man and the other definitive hosts, become infected by consuming viable metacercariae in the flesh of the fish; the metacercariae excyst in the duodenum, ascend the common bile duct,

and mount up the bile capillaries where they finally lodge and mature The number of adult worms in a case of heavy infestation is very large

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The infection occurs only in the Far East, in some parts of which it is very prevalent It is endemic throughout most of China and in Indo-China, Formosa, Korea and Japan.

AETIOLOGY

Clonorchis sinensis has been recovered from the livers of man, of the dog, of the cat, and of a number of other animals The adult flukes measure from 10 to 25 mm in length and from 3 to 5 mm in breadth They contain both male and female genitalia The golden-brown *operculated eggs are of a truncated ovoid shape and measure from 27* to 35 μ by 11 to 20 μ; they are mature when discharged in the stools, each containing a miracidium. Miracidia emerge from the eggs when they are ingested by certain water-snails of several genera. After a [illegible]

[illegible]

coming metacercariae Man and the other definitive hosts, become infected by consuming viable metacercariae in the flesh of the fish; the metacercariae excyst in the duodenum, ascend the common bile duct,

metacercariae in the muscles Man and other animals including the cat and the dog become infected on eating raw fish flesh The metacercariae excyst in the duodenum and the larvae migrate up the ampulla of Vater to the distal ducts where they attach themselves and mature Eggs escape back to the faeces about 4 months after infection

The pattern of pathological changes resembles that of clonorchiasis, but advanced periportal hepatic cirrhosis and associated syndromes are much less common Concretions about masses of eggs and debris in the dilated and distended bile ducts and gall bladder frequently cause signs of obstructive cholangitis and cholecystitis

Diagnosis is based on the recovery of the eggs in faeces or duodenal juice or on skin tests similar to those used for the detection of clonorchis infection

TREATMENT OF FLUKE INFECTIONS

Chloroquine has been used successfully in both paragonimiasis and clonorchiasis, it is being tried in opisthorchiasis It is clinically ineffective in cases of cirrhosis, in which the administration of choline may bring some relief

Dosages required vary widely A course of 1½ to 2 tablets twice daily for two weeks, followed by 1½ to 2 tablets thrice weekly for a total of up to 5 weeks may influence the infection and sometimes cure clonorchiasis where the egg output does not exceed a million per day The drug is believed to act on the adults in the bile ducts but the eggs show morphological changes soon after the beginning of treatment Similar doses

oral glucose and mixed vitamins of the B group Nausea and anorexia predominate, with consequent loss in weight Some patients complain of dizziness and vertigo Headache and insomnia are common. There may be allergic pruritus or skin reactions No ocular symptoms or changes in the leucocyte or erythrocyte counts have been reported

FLUKES, INTESTINAL

These trematodes are widely distributed in wild and domestic animals and infection of man is often only accidental Their life-cycles

Prophylaxis consists of the proper cooking before consumption of all fresh-water fish in the areas of endemicity of the parasite. Eating raw, salted, pickled or partially cooked fish may lead to infection.

FASCIOLA HEPATICA

The non-embryonated operculated *eggs of the sheep liver fluke are* passed in the sheep faeces Miracidia escape in water in 10 to 15 days and invade *Lymnae* snails Cercariae are produced in a week, escape and

to reach the bile ducts via the liver parenchyma and periportal connective tissue Adults mature in the biliary tract about 4 months after infection

Pathological changes occur in the walls of the invaded bile ducts. The epithelium hypertrophies and desquamates, the duct wall hypertrophies and later fibroses Cystic dilatations of the duct are formed and adults erode with masses of eggs into the parenchyma, setting up granulomatous reactions and later fibrosis. Abscesses commonly form about the eggs The liver at first enlarges. Later it shrinks as cirrhosis develops After many years the complications of cirrhosis, including portal hypertension, may develop

Ectopic larvae may be distributed to any tissue so that adults and associated lesions may be found in the blood vessels, the brain, the orbit or in subcutaneous abscesses

Pharyngeal fascioliasis (*halzoum*) is described in the Middle East, resulting from the lodgement of adults in the mucosa following the eating of mutton or goat flesh Serious obstruction of the air passage may result

General reactions to the infection may be severe and include fever, coughing, abdominal pain and tenderness in the right hypochondrium or over the gall bladder, persistent diarrhoea, vomiting of bile-stained fluid and frequent sweating. There may be anaemia and leucocytosis Eosinophilia is high

Diagnosis is made by the discovery of the eggs in the faeces or by complement fixation tests and skin reactions using specific antigens made from adult worms.

OPISTHORCHIS FELINEUS

Infection with this worm leads to opisthorciasis It occurs in North Eastern Europe, the USSR, India, Thailand and Japan

The pathological changes in the host are confined to the intestine and are similar to those induced by *Fasciolopsis*

Heterophyes heterophyes

The adult measures about a quarter of an inch and is attached to the wall of the small intestine The eggs, each of which contain a fully developed miracidium, are passed in the faeces Man is infected by eating raw fish flesh containing metacercariae

Mild inflammatory cellular reactions appear at the point of attachment of the worms and in areas in which the adult has invaded the mucosa Superficial necrosis of the mucosa occurs with excess mucus secretion Diarrhoea results Occasionally the eggs reach the mesenteric lymphatics and pass to the brain and the heart, in the latter they cause tissue responses involving the myocardium and cardiac valves *Heterophyes katsuradai*, which occurs in Japan, produces similar effects.

the wall of the duodenum It may penetrate the mucosa and oviposit in the submucosal tissues Mature eggs are passed in the faeces Man becomes infected by eating raw or inadequately cooked fish flesh Other members of the family may establish themselves in many definitive hosts, including man, the second intermediate hosts are usually fish but may be frogs or shrimps

The pathological processes induced by these infections are much the same as in infection with *Heterophyes* spp , except that the adults invade the deeper layers of the mucosa possibly because they are incompletely adapted to man Eosinophilic and polymorphic infiltrations of the intestinal wall associated with erosion of the mucosa and excessive mucus secretion occur at or near the site of attachment or about eggs laid in the submucosal tissues

Eggs may reach the intestinal venules and lymphatics and get carried to the brain, spinal cord and the heart, where they initiate granulomatous reactions giving rise to local damage and functional disturbances There is often relatively little tissue reaction to the invasion of the mucosal tissues by the adults, which never undergo effective encapsulation

FLUKE THE 'LUNG'
PARAGONIMUS WESTERMANI

Endemic haemoptysis is a condition due to infestation of the lungs with the trematode parasite *Paragonimus westermani* The resultant

have many points in common. Adults are leaf-shaped hermaphrodite motile worms varying in length from minute to several inches. They are attached by muscular suckers to the intestinal wall. Eggs, which are operculate and contain an undeveloped ovum, are passed in the faeces. After 2 to 3 weeks hatching takes place either in water or in a fresh-water mollusc intermediate host and the miracidia escapes to infect an appropriate snail, from which cercariae are eventually discharged. These encyst to form metacercariae either on vegetation or in the next host, usually a reptile, fish or a second mollusc. Man is infected by ingesting the metacercariae. The larva is released in the small intestine and matures into the adult.

Two sub-orders occur in man, namely *Amphistomata* and *Distomata*. *The former are relatively unimportant clinically. Watsonius Watsoni* has been reported only once in man, but *Gastrodiscoides hominis* occurs fairly frequently in India where it is a natural infection of the pig. In man it is found in the caecum and ascending colon and gives rise in heavy infections to mucous dysentery or diarrhoea

The more important *Distomata* are discussed below·

Fasciolopsis buski

This is a common parasite of man and pigs and occasionally of dogs in China, Taiwan, Thailand and elsewhere in the Far East.

Adults measure up to 7 cm long and are normally attached to the duodenal and jejunal mucosa In very heavy infections they may be present in the stomach and the large intestine. Man is infected by ingesting metacercariae encysted on the roots of the lotus and on the water caltrop Adults mature in the small intestine in about three months Eggs are passed in the faeces

The large flukes cause direct damage to the intestinal wall Inflammatory cellular reactions and local accumulations of eosinophils appear at the point of attachment where ulceration and abscesses sometimes follow Haemorrhage may occasionally occur as a result of erosion of mucosal vessels Excessive secretion of mucus is common in heavy infections Local obstruction of the gut has also been recorded

The 'toxic' effects of infection are severe. Oedema of presumably allergic origin occurs in the face and legs and ascites is common

Echinostoma ilocanum

The adult is about half an inch long and is attached to the jejunal wall. Eggs are passed in the faeces. Man is infected by eating molluscs (snails and clams) containing metacercariae.

CLINICAL PICTURE

At the time of infestation with, and of the migration of, the metacercariae there are no symptoms The onset of symptoms is associated with the development of the inflammatory reaction around the parasites and their eggs in the tissues Usually it is insidious, but there may be some initial fever There is a cough, which soon is associated with increased expectoration of a sputum which is viscous and flecked with blood There may be haemoptysis after a spasm of coughing, which often is associated with severe pain in the chest There is increasing



FIG 62
Paragonimus infection in a Chinese seaman Tomograph shows cyst in lung Eggs in purulent sputum
(Courtesy of *British Journal of Radiology*)

shortness of breath, with evidence of a progressive bronchitis and bronchiectasis, there may be a pleural effusion, and, as the condition continues, there is increasing radiological evidence of fibrosis in the lungs

The symptoms caused by the presence of parasites in the abdomen vary with their location Those present in the walls of the intestine cause symptoms of enteritis, those in the liver of hepatitis, those in lymph glands may lead to abscess formation, those parasites in the abdominal wall or skin tend to discharge their ova by rupture of their containing capsules to the exterior In the central nervous system the

disease is characterized by an insidious onset, cough with the expectoration of blood-tinged sputum containing ova, pains in the chest and dyspnoea, bronchiectasis and fibrosis of the lung tissue

GEOGRAPHICAL DISTRIBUTION

Paragonimiasis of man occurs throughout the Far East; sporadic cases of infection have been recorded in South America; there is evidence that it is prevalent in localized areas of West Africa and the Belgian Congo

AETIOLOGY

Paragonimus westermani has been recovered from the lungs of man, of many carnivora, and of some other animals. The adult flukes measure from 7.5 to 12 mm in length, 4 to 6 mm in breadth, and 3.5 to 5 mm in thickness. They contain both male and female genitalia, and produce oval golden-brown-coloured operculated eggs measuring from 80 to 120 µ by 60 to 80 µ. The immature eggs classically are expectorated with the sputum, or are swallowed with it and are passed in the faeces. After their escape they mature in water over a period of some weeks; a larva (miracidium) then emerges from each and enters one or other of several species of snails of the genus *Melania*. Within the liver glands of the snail there is a multiplicative cycle of development, with the production finally of cercariae. The cercariae emerging from the snail enter into crayfish or crabs; in these they encyst in the muscles and other tissues and grow into metacercariae. Man, and the other definitive hosts, become infected by consuming viable metacercariae in these creatures; on being swallowed the metacercariae excyst in the small intestine, penetrate its wall and, it is stated, actively pass through the abdominal cavity, the diaphragm, and the pleura into the lungs, where they lodge peripherally. A cyst-like capsule of inflammatory and fibrous tissue forms around each parasite. Within six weeks the parasites reach maturity and start producing eggs. The capsule swells and ruptures into a bronchiole; the contained eggs, together with inflammatory cells and blood, are expectorated in the sputum. It is unusual for more than twenty parasites to be present in human lungs. In addition to the site of election, the lungs, aberrant flukes may lodge in the liver, the walls of the intestine, the peritoneum and mesentery, the abdominal lymph glands, the muscle or skin of the abdominal wall, the diaphragm and the pleura. In addition they have been recovered from organs remote from the abdomen or the chest, such as the brain and cord, their presence in the latter sites causes various manifestations of injury to the central nervous system.

CLINICAL PICTURE

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parasites may give rise to Jacksonian attacks, encephalitis, meningitis, and myelitis with palsies of various types

Though the symptoms of paragonimiasis are most severe during the first six or seven years of infection, fresh symptoms may continue to appear for the twenty years that some of the parasites survive.

DIAGNOSIS

This is established only on recovery and identification of the characteristic eggs In the sputum masses of eggs can often be picked out as faintly-seen rust-brown points Parasites lodged in the superficial tissues of the abdominal wall may be removed by biopsy. Ova may sometimes be found, if carefully sought for, in the stools in those cases where there are intra-abdominal lesions

X-rays of the lungs do not afford a definitive diagnosis of the condition, but yield information of value in assessing its extent and progress.

TREATMENT

[illegible] ing the inf[illegible] treatment[illegible] for at least 10 days, is said to destroy these flukes The treatment is by no means invariably successful

CYCLOPHYLLIDEAN TAPEWORMS

INTRODUCTION

A number of cestode parasites have been recorded as parasites of man Some of them are relatively common, and of these a few pass one stage of their life cycles as strictly human parasites, some are parasitic in other animals and occur only incidentally in man. The commonest cestode parasites of man in the tropics and subtropics are the large cyclophyllidean tapeworms *Taenia saginata* and *T. solium*, and the dwarf tapeworms *Hymenolepis nana* and *H. diminuta*

With the notable exception of *T. solium*, of which both the adult and the larval stages may infest man, the worms mentioned occur in him solely in the adult stage as intestinal parasites. It is very doubtful if their presence in the bowel habitually causes symptoms of consequence, or that any material ill-health results from it. Infestations with the large tapeworms usually are single and only rarely are multiple; in the case of the dwarf tapeworms commonly they are multiple The adult

worms attach themselves by their heads to the mucosa of the small intestine only for the purpose of anchorage They have no buccal cavity or alimentary tract and, therefore, they do not suck blood or other nutriment from the point of their attachment The strobila hangs down from its head within the lumen of the intestine The worms derive their sustenance by surface absorption from the intestinal contents with which they are in contact It has been claimed that in particularly susceptible persons the presence of tapeworms may cause the appearance of allergic manifestations, possibly due to absorption of the metabolites of the worms, but if this is indeed the case such symptoms are rarely seen in otherwise healthy persons The presence of an adult tapeworm infestation of the bowel is usually brought to the notice of the patient by the passage of segments of the worm

TAENIA SAGINATA

This, the common beef tapeworm, occurs in beef-eating peoples all over the world irrespectively of climate The adult worm is a strict [illegible] pin-head size, is provided with four sucking discs (but no hooks) by means of which it adheres to the mucosa of the upper small intestine From the neck immature segments continuously develop, as these immature segments are pushed down the body by the formation of fresh segments they grow in size, and develop within them both male and female organs The male organs of a mature segment fertilize the female organs in an adjacent mature segment, the testes then degenerate The uterus of the fertilized segments becomes loaded with morphologically characteristic eggs The gravid segments are barrel-shaped muscular structures which break off from the lower end of the worm singly or in groups of two or three, these for a time contract and writhe on escaping to the exterior through the anus Not uncommonly they issue from the anus unexpectedly, or they may be passed with the stools It is on seeing the extruded segments that the patient becomes aware of his infestation

After obtaining muscular relaxation of an extruded segment, by immersion in water for half an hour, a central-stemmed uterus, with fifteen to twenty lateral branches containing many eggs, and with a lateral pore, can be seen if it is firmly squeezed between two glass slides By this means a diagnosis not only of the presence of the parasite but of its species can be established It is important to differentiate a harmless *T. saginata* from the potentially highly dangerous *T solium* infestation

The gravid segments of *T saginata* when voided disintegrate and liberate their contained eggs The eggs survive for some time but perish unless swallowed by cattle; in the tissues of bovidae they give rise to cysticerci, each containing the head of a future worm in a small cyst. The beef is now 'measly'; it is the consumption by man of viable cysticerci (*Cysticercus bovis*) in beef that results in his developing an intestinal infestation with *T. saginata*. The infestation in man is usually by a single worm, but sometimes several may be found in a single individual. The diagnosis is made by looking for extruded gravid segments, only exceptionally, when a segment is ruptured in them, will the eggs be seen in the stools.

TREATMENT

To remove a tapeworm from the bowel an anthelmintic must come into contact with its head, its action ideally should be purely a local one on the worm, and the drug should not be absorbed by the host. The head of the [illegible]
the exterior, if [illegible]
worm are remov[illegible]
worm to its full size within a few months.

The drug traditionally used for eradication of a tapeworm infestation is male fern; it is given as an ethereal extract of filix mas The total dosage is 90 minims; this is best divided into three doses given at half-hour intervals The patient is starved for 48 hours, he is then given a small saline purge the night before treatment Two hours after the end of treatment he is given a large saline purge (1 to 2 oz of magnesium sulphate) to expel the drug and the worm All stools over the next [illegible]

may cause vomiting; it may cause severe toxicity in rare cases; it is effective in about half the cases treated with it.

[illegible]

pended in 100 ml of warm water and introduced down the tube from a syringe. Half an hour later $1\frac{1}{2}$ to 2 oz of magnesium sulphate in warm water is similarly introduced, and the tube is withdrawn A warm drink [illegible]

dosage

Dichloropen and its associated derivatives, which for some time have been used in veterinary practice, are taenicides also suitable for use in man The dosage is 0 5 gm per 16 lb body weight, given as a single dose, this need not be preceded by lengthy starvation or be followed by purgation The drug digests the immature and upper segments of the

months have elapsed after the treatment

The incidence of any illness associated with high fever is sometimes associated with the spontaneous dislodgement of a tapeworm

TAENIA SOLIUM

This worm in its developmental stages superficially much resembles *T saginata* The adult is a strict parasite of man, but in contradistinction to *T saginata* the larval cysticercoid stage while it normally occurs in the pig unfortunately also can develop in man It is this fact which renders infestation, or even contact, with the parasite potentially so highly dangerous

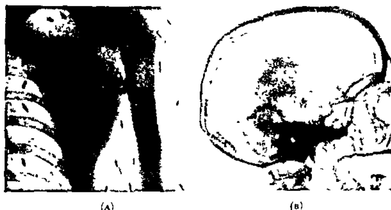
The adult worm differs from that of *T saginata* in that the head is armed with hooks in addition to four suckers, the worm is slightly smaller, and the gravid segments are more squat and contain a central stemmed uterus with less than a dozen lateral branches The eggs contained in the gravid segments of either species morphologically are identical

Infestation with the adult worm follows the consumption of viable cysticerci (*Cysticercus cellulosae*) in measly pork The contained heads attach themselves to the mucosa of the upper small bowel and segments grow from the neck The gravid segments are passed through the anus, it is those eggs which are consumed by pigs that ensure the maintenance of the parasite

If man swallows eggs liberated from disintegrating gravid segments of his own or another's intestinal worm, like the pig he develops cysticercosis The larvae liberated from the eggs penetrate the mucosa of the small bowel and are carried in the circulation to various tissues where they encyst and form cysticerci Light human infestations, the result of swallowing a few eggs, possibly are fairly frequent but escape notice unless a cyst is so located that it causes physical signs Heavy infestations, with hundreds of cysticerci, cause very grave manifestations chiefly due to the presence of the cysticerci in the central nervous system

The cysticerci in man lodge in the connective tissues, voluntary muscles, and the central nervous system While alive they rarely cause

trouble, but they begin to die and degenerate within three to five years Those dying in muscle often calcify and can then be seen radiologically Those dying in the central nervous system very rarely calcify and so cannot be seen radiologically; but as they degenerate they swell and cause disintegrating cellular changes in the surrounding nerve tissue. These result in a wide range of clinical manifestations, such as Jacksonian attacks, psychical disturbances and mental deterioration. Cerebral cysticercosis is a grave condition; the prognosis is a bad one, as with the death of increasing numbers of cysticerci over a period of years the effects tend to be cumulative.



(A) (B)

FIG 63 *Taenia solium* cysticercosis Dead cysts calcified in musculature (A), but not calcified in brain (B).
[From E Noble Chamberlain, *A Textbook of Medicine*, John Wright & Sons Ltd, Bristol, 1951]

One explanation sometimes advanced for the massive infection with cysticerci seen in certain individuals is that such individuals actually harboured an intestinal infestation with an adult *T solium* By retroperistalsis, during some temporary intestinal disorder, one or more gravid segments have been carried back up the small bowel, they disintegrated and the contained eggs liberated their embryos which penetrated the bowel wall, so causing the extremely heavy infection.

DIAGNOSIS

The diagnosis of an infestation with an adult tapeworm is made by recovery and identification of the gravid segments passed out of the bowel

A diagnosis of cysticercosis is made by the palpation of cysticerci, usually in the subcutaneous tissues; by biopsy of these and identifica-

tion of the hooked head of the future worm in each of them, and by X-raying the general musculature and seeing calcified cysticerci in it X-ray of the skull usually reveals nothing of specific significance

TREATMENT

The eradication of the adult worms from the intestine is attempted along the lines indicated in the treatment for *T saginata* infestation The treatment should not be delayed when this infestation is detected; every precaution must be taken to ensure that dissemination of the eggs cannot occur

The treatment of cerebral cysticercosis is palliative Jacksonian epilepsy is controlled by sedatives such as the barbiturates An individual cyst causing a localizing lesion may be removed from the brain, but this is rarely practicable

HYMENOLEPIS NANA AND H DIMINUTA

The dwarf tapeworms are common and are cosmopolitan in their distribution throughout the subtropics and tropics *H nana* is a small

eggs, and there is no cycle of larval development in an intermediate host In addition to man, rats and mice harbour this parasite, but murine strains of the parasite do not usually cause a human infection, the human strains are passed from man to man The infection commonly is with a number of worms, very heavy infections with *H nana* sometimes occur, possibly as a result of internal autoinfection Such heavy infections are stated at times to cause severe toxaemia, diarrhoea, nervous manifestations and even convulsions in very young children in whom especially they are found

H diminuta is a common parasite of rats, mice and other similar small rodents It not uncommonly is found in man It is rather larger than *H nana*, and its maximum diameter is about 4 mm. It further differs from that worm in requiring an intermediate arthropod host for the development of its larval stage, which is a cysticercoid The rat flea

in the stools

The treatment used for the other tapeworm infestations readily causes removal of these worms

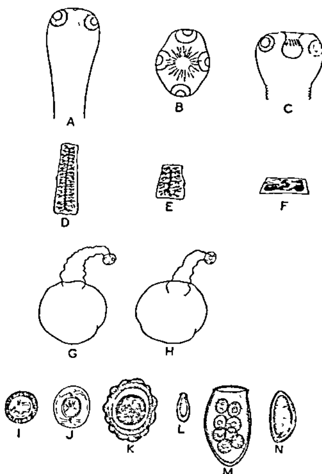


Fig 64

A. [illegible]
B
C
D.
E
F
G
H [illegible] 3)
I
J *Hymenolepis nana* egg
K *Ascaris* egg
L *Clonorchis* egg
M *Paragonimus* egg
N *Enterobius* egg
(I – N × 330)

ECHINOCOCCUS GRANULOSUS (HYDATID) AND E MULTILOCULARIS

The adult worm lives in the small intestine of the definitive host (dog, jackal, wolf, cat) which itself becomes infected by ingesting larva-containing viscera of intermediate hosts, especially sheep and cattle Eggs are discharged in the faeces of the definitive host and are swallowed by man either as a result of direct contamination or following contact with dogs or other infected animals

Oncospheres hatch out in the duodenum and the larvae migrate through the wall, reaching the mesenteric vessels and eventually becoming lodged in tissue capillaries, especially in the liver, and less frequently, in the lungs A few larvae (often only one or two) survive in the tissues and go on, over months and years, to form the characteristic 'hydatid cysts'

These are unilocular cysts with a double wall composed of an outer laminated layer and an inner nucleated 'germinal' layer From the latter, as the cyst grows, are budded rounded cellular masses, which eventually become cystic These are the 'brood capsules', from the inner wall of which scolices with rostellar hooklets bud and invaginate Brood capsules may remain attached to the parent cyst wall or float free in its milky fluid contents as the so-called 'hydatid sand' Some cysts are sterile and may never produce brood capsules, others never produce scolices If the wall of the original cyst (the 'mother' cyst) is ruptured, some of the brood capsules escape as exogenous or 'daughter' cysts and become seeded in contiguous tissues

Cysts are unilocular in the vast majority of cases except in certain geographical regions where multilocular cysts occur (called alveolar hydatids) These are now believed to result from infection with a separate species *Echinococcus multilocularis*, which infects small wild carnivores and rodents

In the multilocular form of the infection the tissue cellular reactions are more vigorous, but there is less fibrous reaction Cysts contain multiple small cavities with scanty fluid containing discoloured crumpled

pressure effects due to the cyst and from immunosensitivity reactions resulting from the host reaction to the worm

On lodgement in the tissues the larva becomes surrounded by cellular infiltration, consisting of lymphocytes, plasma cells and eosinophils. Later, cellular fibrous tissue envelopes the cyst as a capsule The cyst wall may eventually calcify Pus is produced only when the dead larva has become secondarily infected

In the tissues where the cysts are developing local damage occurs

the same tissues or in other areas, may cause early clinical signs Cysts developing in bone tend to become syncitial and invade the bone structure, leading to erosion, cavitation and sometimes spontaneous fracture.

Hydatid of the liver sometimes leads to hepatomegaly which is often symptomless, but must nevertheless be differentiated from amoebic liver involvement or hepatic tumour

Compression signs are particularly common in the lungs, where they are frequently accompanied by pleural effusion Rupture of the cyst into the bronchi may lead to relief or set off an anaphylactic reaction

Ectopic spread of 'daughter' cysts may occur after rupture of a 'mother' cyst, leading to localizing lesions in the brain and elsewhere.

in

is

may develop, however, if there is leakage of cyst fluid, following rupture or surgical interference

Eosinophilia is appreciable and persistent, varying from 10 to 25 per cent, and rising sharply in 'anaphylactic' episodes. Complement-fixing antibodies and precipitins can be demonstrated in the blood serum, using as antigen sterile hydatid cyst fluid or alcoholic extract of brood capsules

DIAGNOSIS AND TREATMENT

The antigens referred to above may also be used for a highly specific diagnostic skin test, the Casoni reaction, to perform which 0 1 ml of antigen is injected intradermally into the arm of the suspected individual A positive reaction develops in about 20 minutes as a large wheal several cm in diameter, with many pseudopodia, and always surrounded by a brilliant red arteriolar flare

hydatid larvae, the latter much less so.

X-ray examination of the suspected tissues is often helpful, especially in late cases where the cyst wall may be calcified, and in hydatid of bone, in which bone tissue is distorted and riddled with cavities; there may be spontaneous fractures

Most cases require surgical treatment Exploration should not be carried out unless everything is prepared for full interference Operative

procedure aims at removal of the aspired cyst (often re-filled with a weak solution of formalin), with suitable precautions for preventing contamination of the tissues by the contents, an accident that may lead to severe anaphylaxis

Attempts have been made in some inoperable cases to desensitize the patient over a long period by injection of antigens

Anthelminthic drugs are useless

PSEUDOPHYLLIDEAN TAPEWORMS

DIPHYLLOBOTHRIUM LATUM

The eggs are discharged in the faeces of humans infected with the adult worms They mature in water for about two weeks and hatch an oncosphere which is taken up by a copepod, usually *Cyclops* spp , in the hoemocoele of which the procercoid stage evolves The copepod is ingested by a fresh water fish in the muscles of which the plerocercoid or sparganum larva develops Man becomes infected by ingesting uncooked fish flesh containing spargana The adult worm, which may reach 30 feet in length, matures in about three months It inhabits the small intestine, to the mucosa of which it is attached by a small hookless scolex Multiple infections are common Other hosts include the dog, the cat and the pig

In multiple infections there may be mechanical intestinal irritation and occasionally obstruction Systemic 'toxic' effects may be considerable and include abdominal pain and discomfort and diarrhoea Emaciation may result, 'convulsions' are common in children Allergic manifestations are common, including a high degree of eosinophilia and localized oedema The blood white cell count is frequently raised

In some cases megaloblastic anaemia resembling pernicious anaemia may be present, possibly as a result of competition between the worm and the host for vitamin B12 The administration of extracts of adult worms, which contain large amounts of vitamin B12, or the exhibition of Castle's extrinsic factor will relieve the anaemia The administration of folic acid may also prove successful

Diagnosis is made by indentification of the eggs in the faeces or of the adult worm after treatment with anthelminthics

The adults may be effectively removed by dosage with filix mas or mepacrine (See p 502)

DIPHYLLOBOTHRIUM (SPARGANUM) MANSONI

Ingestion by man of copepods infected with procercoid larvae of other pseudophyllidean tape worms, consumption of raw fish, frog,

fowl or snake flesh containing already developed sparganum larvae (derived from several worms grouped together as *Sparganum mansoni*) or direct contact with flesh containing spargana (for instance the use of raw frog meat as a poultice) may be followed by the appearance of spargana (sparganosis) in almost any tissue except bone. There is some lymphocytic and eosinophilic infiltration about the actively moving larva. After its death the cellular response increases and the worm becomes replaced by caseous or purulent material. The larvae usually lie in the connective tissue planes especially in the subcutaneous and orbital tissues. The affected region is swollen and intensely painful. Elephantiasis may result from lymphatic obstruction subsequent to involvement of the local glands.

Treatment is local. Injection into orbital lesions of 2 to 4 ml of 40 per cent ethyl alcohol plus a local anaesthetic such as epinephrine-free procaine is said to be effective. Subcutaneous single lesions may be excised. In infections with one form of larva which proliferates by branching, extensive lesions may develop and local treatment is impracticable. Some success has been claimed for standard intravenous courses of novarsenobenzol.

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YAWS

DEFINITION

FRAMBOESIA, pian A contagious disease caused by *Treponema pertenue* characterized by lesions in the skin and bones which are granulomatous in the early stages and later destructive

GEOGRAPHICAL DISTRIBUTION

The disease is unevenly distributed within the tropics It is very common in northern South America, the West Indies, north and equatorial Africa, parts of India, Burma, Indo-China, Siam, Malaya, the East Indies, the Philippines It also occurs in Panama, Mexico, Northern Australia and Ceylon In the latter it is at present largely limited by control measures It was once common in the United States

Yaws is commoner in rural districts than in towns or cities

AETIOLOGY

The causative organism The organism *Treponema pertenue* is a motile spirochaete about 20 µ long and having 8 to 20 corkscrew spirals It is morphologically indistinguishable from the causative organisms of syphilis (*T pallidum*) and Pinta (*T carateum*) It has not been successfully cultivated *in vitro* but can be transmitted to rabbits and monkeys, in which it produces lesions differing somewhat from those initiated by *T pallidum*

TRANSMISSION

The organism is spread chiefly by direct contact with an infective human case It cannot survive for long outside the body, but there is some evidence to suggest that infective material may remain in the soft moist earth floors of native huts for long enough to spread the infection There is no animal reservoir It is believed that the organism cannot penetrate the unbroken skin and that the usual portal of entry is a cut or abrasion In many cases direct contact can easily be traced, in some endemic regions children are deliberately exposed to contact in order to ensure infection

It is believed that in certain districts non-biting flies and cockroaches may occasionally transmit yaws mechanically

Yaws may sometimes have an apparent seasonal incidence, most new cases occurring during the rainy season The disease may remain

quiescent for long periods in some districts, breaking into activity sporadically

It is commoner in hot moist climates than in hot dry. Where it occurs under the latter conditions it is usually less widely spread in the population.

GENERAL

Yaws is most common in sparsely clothed and insanitary agricultural communities Such conditions encourage transmission by contact. It is relatively uncommon in towns and cities. The reverse is true for syphilis, which is much commoner in urban districts.

Yaws is most commonly acquired in young childhood. Infants under one year old are rarely affected; congenital transmission has not been satisfactorily demonstrated.

The majority of cases occur before puberty. The disease may be acquired by non-immune adults who have not had it in childhood Yaws in adults is, however, usually a manifestation of earlier infection.

Coloured races are much more frequently infected than white This is probably due mainly to difference in standards of hygiene.

IMMUNITY

An attack of yaws may confer some resistance to a further infection It tends to persist even after the active disease has ceased, but it is not always complete; for instance, a mother may become reinfected from the child while suckling. Treatment may also interfere with the progress or development of immunity and be followed by reinfection.

There is evidence of cross-immunity between yaws and syphilis. Individuals who have acquired yaws and developed an immunity to it

Serological reactions are mentioned under the section on laboratory diagnosis

CLASSIFICATION

In what follows the terms 'primary', 'secondary' and 'tertiary' are used to describe the lesions of yaws The adjective 'primary' in relation to the initial lesion in yaws is self-explanatory Opinion is divided, however, concerning the use of 'secondary' and 'tertiary' So long as the classification is made in terms of the nature and behaviour of the

which justify their separation The important distinction to the clini-

scarring or involving surrounding structure, whereas the tertiary granuloma is progressive and involves contiguous tissues leading to destruction, scarring and deformity Secondary and tertiary lesions of bones differ in similar respects, the former being non-destructive and likely to resolve spontaneously, the latter destructive and permanent

Tertiary lesions occur late in the disease and are never present contemporaneously with secondary lesions, the latter do not appear after the development of tertiary lesions

Alternative classifications for the skin lesions of yaws have been recently suggested by the World Health Organization on the grounds that no clear separation can be made in time between the secondary and tertiary skin lesions In these classifications the differences inherent in the behaviour and infectivity of the lesions are ignored The word 'yaws' is abandoned for the more widely used term 'framboesia' The primary lesion is called the 'initial framboesioma', and the various skin lesions which develop subsequently are referred to as 'framboesides' in keeping with the use of 'syphilides' in describing syphilitic skin lesions The lesions are distinguished as 'early' or 'late'

PATHOLOGY

The basic lesion in yaws is a granuloma In the primary phase the lesion arises at the site of infection Subsequent manifestations presumably result from distribution of the organism in the blood stream The treponema can be found in the primary lesion and in most typical secondary lesions, except those of bone It cannot as a rule be isolated from tertiary lesions

Lesions arise in either the skin and subcutaneous tissues or in bone In primary and secondary skin yaws the deeper structures are not usually involved, as they are in the later stages Visceral lesions have been described by some authors but occur very rarely if at all The central

site depends on the thickness of the epithelium and the looseness or otherwise of the underlying tissue

In its earliest stages the epidermis is slightly thickened and the underlying tissue is loosely infiltrated with lymphocytes and plasma cells As the lesion progresses it forms a papule in which the epithelium is thickened, and hypertrophied branching epithelial papillae project

deep into the corium The granulomatous tissue develops immediately beneath the epithelium There is usually some oedema of the corium especially in the interpapillary spaces and the connective tissue beneath this region is closely infiltrated with lymphocytes and plasma cells and sometimes scattered polymorphs and eosinophils. Epithelioid and giant cells may be present in well established lesions. The local blood vessels may [illegible]

Th[illegible]
thins [illegible]
ulcerate, especially those situated in moist areas The surface of the ulcer is criss-crossed and patterned with pale areas formed by the remains of epithelial papillae, between which granulomatous tissue wells up as pale reddened areas which bleed easily The exuded serous fluid eventually coagulates over the surface, which is partly covered with epithelium.

Treponemata are numerous in the upper regions of the lesion, they are not usually present in the crust formed after ulceration

The edges of the lesion are formed by raised slightly hyperkeratotic epithelium in which the cells are frequently oedematous and degenerate

Unless there is secondary sepsis, healing is followed by restoration of the epithelium of any ulcerated area and eventually by recovery of pigmentation Primary lesions may leave a thin tissue paper scar, otherwise they heal without scarring. The small lesions of secondary yaws frequently heal without scarring.

The granulomata of the later stages of yaws are similar to those of the early stages but the process spreads to involve deep tissues and the histological picture becomes complicated by the development of proliferating fibrous tissue, epithelioid cells and sometimes giant cells There may be more noticeable changes in the small blood vessels with perivascular cellular infiltration and some endothelial proliferation

Lesions in bone occur both early and late in the disease. The early changes are conveniently included in the secondary stage of the disease Treponemata have not been recovered from such bony lesions

The principal active bone lesions in secondary yaws are rarefaction, particularly in the cortex of long bones, and periostitis with deposit of new bone Rarefaction may be diffuse or focal, and involve the periosteal deposits. Secondary bone changes tend to involve several bones at the same time.

Ulceration of the skin overlying secondary bone lesions is unusual Organization of periosteal deposits and thickening of the cortex associated with bony expansion (especially in the bones of the legs) may remain after resolution of the lesions

Active bone lesions may reappear during relapses of the disease and be followed by the same restoring processes, so that the clinical picture

present in a given case may be the result of repeated progress and recession of the lesions

Later bony lesions are usually classified as tertiary and include well defined foci of rarefaction, especially in the cortex of long bones Localized areas of periostitis with periosteal deposit of bone may occur in the region of these rarefactions Tertiary lesions are destructive and may lead to deformity and sinus formation They are usually confined to a few bones only, unlike secondary lesions which tend to be multiple

CLINICAL PICTURE

INCUBATION PERIOD AND PRIMARY LESION

The primary lesion appears 3 to 6 weeks after exposure During this period there may be some headache, vague pains in the limbs, joints and muscles and, towards the end, some mild fever The fever may continue after the appearance of the lesion and may reappear during the early stages of the secondary phase

The site of the initial lesion varies It is most common on the legs or buttocks in areas where trauma is likely to occur It may occasionally commence in an already ulcerated region, for instance, in a tropical ulcer

The early stages of the primary lesion are not often seen It appears first as a small erythematous macule which is slightly infiltrated Within a few days a papule is formed or sometimes a group of papules

as a thin yellowish film forming a yellow or grey crust over the lesion After some weeks or months the non-ulcerated yaw heals completely In ulcerated lesions scabs are formed under which the epithelium is eventually restored A thin light-coloured tissue paper scar is sometimes left.

The lesion is usually painless, it may be itchy and scratching may lead to secondary infection.

Local lymph glands may be enlarged, discrete and tender, especially if secondary infection has developed

The primary yaw is often still active when the secondary lesions first appear and may persist throughout the secondary period

SECONDARY SKIN LESIONS

In the untreated case secondary lesions usually appear in a few weeks or months after the appearance of the primary lesion They may be associated with general constitutional disturbances similar to those sometimes accompanying the appearance of the primary lesion.

deep into the corium. The granulomatous tissue develops immediately *beneath the epithelium There is usually some oedema of the corium* especially in the interpapillary spaces and the connective tissue beneath this region is closely infiltrated with lymphocytes and plasma cells and sometimes scattered polymorphs and eosinophils Epithelioid and giant cells may be present in well established lesions. The local blood vessels may be cuffed with lymphocytes, the endothelium is often unchanged.

The infiltration progresses and eventually the overlying epithelium thins Most lesions remain covered with epithelium, but some may ulcerate, especially those situated in moist areas The surface of the ulcer is criss-crossed and patterned with pale areas formed by the remains of epithelial papillae, between which granulomatous tissue wells up as pale reddened areas which bleed easily. The exuded serous fluid eventually coagulates over the surface, which is partly covered with epithelium

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In the majority of cases the secondary eruption closely resembles the primary, except that individual lesions are somewhat smaller The lesions may be single or multiple, grouped round the region of the primary yaw or scattered in irregular groups over the body There may be one or many They often appear in successive crops A second crop may appear before the first has healed, so that lesions in various stages of evolution may be present at the same time

Lesions may occur anywhere on the skin They are most commonly found on the face, especially around the mouth, in the axillae, the *vulval cleft, the anus or on the buttocks They are rare on the scalp* They are frequent at mucocutaneous junctions but uncommon on mucous membranes proper, although they may be seen on the palate

Their appearance and development are similar to those of the primary yaw An erythematous macule is followed by a papule with an irregular puckered surface covered by thin intact epithelium Ulceration may occur and crusts form which may be secondarily infected, especially near moist surfaces such as the mouth or vulva Crops of lesions may appear and progress simultaneously, or in relays Individual lesions may last only a few weeks or many months Lesions frequently never ulcerate but remain lightly covered with epithelium throughout their development

The secondary lesion tends to heal spontaneously in due course and leave somewhat depigmented areas with little or no scarring Sometimes the eruption subsides completely for a time and then reappears Quiescent intervals may last weeks or years

Secondary lesions are not usually painful unless they develop in certain special areas where the tissues are unusually firm, such as the soles of the feet and palms of the hands They may, however, be very itchy and secondary infection from scratching is common especially about the mouth and genitalia

Local lymph glands may be enlarged and tender, as a result of secondary infection

The basic granulomatous process is the same in all lesions, but the local effects vary considerably depending on the region affected In the anal or vulval regions, for instance, the lesions are often florid, moist and somewhat flattened with overhanging edges, very closely resembling syphilitic condylomata The most striking effects are, however, seen in the hands and feet In these areas the connective tissue is firm and the epithelium tough, the granulomatous tissue commonly presents on the medial or lateral aspects of the sole where the epithelium is thinner

These lesions are intensely painful and interfere considerably with walking The attempts made by patients so affected to walk on the





FIG. 65 Initial lesion

FIG 66 Typical secondary eruption

[Both Courtesy *Transactions Royal Society of Tropical Medicine and Hygiene*, and Dr C. J. Hackett]

leaving holes This condition is known as 'clavus' The plantar skin is often irregularly thickened, hyperkeratotic, dry, hard, irregularly peeling ('moth eaten') cracked and fissured, secondary infection is common There is often notable irregular depigmentation Lesions in the palm follow the same general course as those in the sole Framboesial onychia may develop on the toes or fingers if the nail bed becomes involved

Florid lesions of the type described above are the commonest secondary lesions They are often the only type of lesion present Sometimes, however, they may be absent or accompanied by other skin lesions which are caused by similar tissue changes, but differ greatly in appearance Occasionally groups of small de-pigmented macules or papules with desquamating boundaries may form and recede without ulceration The site of the papule may become de-pigmented for a time, the colour slowly returning In some cases, especially on the face about the mouth, the lesions may be circinate and closely resemble fungal infections On the anterior aspect of the knees or thighs and sometimes on the abdomen the skin may lose its natural gloss and become leathery, desquamated and peppered with small non-ulcerating papules In some areas, especially on the hands, the local reaction of the epithelium is especially vigorous and hyperkeratosis is extreme, so that small prominences or horns of dry hard epithelium may form and occasionally ulcerate These lesions are commonly painless but may be extremely itchy

The granulomatous process may involve muscle tendons, especially those in the wrist, with the development of prominent painless ganglia which may arise and subside spontaneously

SECONDARY BONE LESIONS

Many cases of yaws undergo spontaneous recovery in the secondary eruptive stage A considerable proportion, however, develop bone lesions These are sometimes the first indication of the disease They are most frequently seen in young children.

Secondary bone changes are usually multiple and involve the whole or most of the shaft of the bone They develop rapidly and resolve spontaneously, usually in a few weeks or months Relapses are common Bones most commonly involved are the long bones of the legs and forearms, especially the ulna Involvement of the bones of the hands is sometimes seen, the picture being that of an acute polydactylitis

The affected areas are tender, painful and often oedematous The local aching and pain are often very severe and the function of the part may be seriously affected

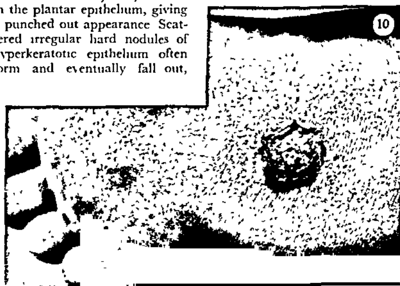
Radiographic examination reveals two main forms of lesions, focal

inner or outer aspects of their soles, depending on which is the more involved, has given the name 'crab yaws' to this particular manifestation of the disease



(a)

Ulceration may also occur directly through the thick plantar skin and is extremely painful and incapacitating In such cases the picture is highly characteristic The granulomatous tissue looks as though it has literally burst through the thickened hyperkeratotic epithelium which is cracked and turned back at the edges of the ulcer In the course of weeks or months the granulomatous tissue may resolve and a considerable cavity may be left in the plantar epithelium, giving a punched out appearance Scattered irregular hard nodules of hyperkeratotic epithelium often form and eventually fall out,



(b)

[(b) Courtesy



Fig. 69 Secondary bone lesions. Clinical aspects
Girl aged 3. Multiple dactylitis and swelling of radius. (See Fig. 68.)
[After C. J. Hackett, *Bone Lesions of Yaws*, Blackwell Scientific Publications, Oxford, 1951]

disappears on healing, or is replaced by dense bone formation, the periosteal deposits may become organized with consequent thickening and irregularity of the bones involved.

Secondary bony changes are rare in the skull except for the involvement of the nasal processes of the maxillary bones, leading to the



(i) (ii)

Fig 68 Bone lesions in yaws

i Secondary lesions (X-ray of case shown in Fig 69

ii Tertiary lesions (Note cortical thickening and areas of rarefaction)

cortical rarefactions and periosteal changes including the deposit of new bone These lesions commonly occur together. The rarefaction

LATE OR TERTIARY LESIONS

These are seen in patients in whom the disease has been allowed to progress untreated or inadequately treated On the whole the tertiary lesions appear some years after the secondary manifestations They may appear in very young children but are not usually observed before the fifth year Most cases with tertiary lesions have a history of having yaws at an earlier age. Occasionally there is no such history, in such cases it is presumed that the earlier stages of the infection have been latent or so mild as to be overlooked

Tertiary lesions, like secondary, are essentially lesions of the skin, subcutaneous tissues and bones The deep viscera and central nervous system are not involved

The tissue reaction, although basically similar to that in secondary lesions, tends to become destructive, rather than resolve Tertiary lesions probably develop as such It is considered unlikely that they result from the persistence and progress of secondary or primary lesions.

A common late lesion is a gummatous granuloma which causes ulceration of the skin and frequently involves the deeper tissues, including bone The lesion is diffuse and may be first noticed as a growing subcutaneous nodule, especially in the legs and other regions where the bones lie close beneath the skin Ulceration is common The ulcer is indolent and slowly progressive, it closely resembles that of late syphilis It may be secondarily infected and eventually heals with heavy scarring and deformity Such scarring is one of the gravest manifestations of the disease

Various other changes occur in skin and subcutaneous tissue which are regarded as tertiary manifestations of yaws These include juxta-articular nodules, which are painless, firm, subcutaneous tumours commonly found in the neighbourhood of the larger joints, particularly the knees

Tertiary palmar and plantar lesions are described in which scarring and contractures may develop The soles show irregular extensive thickening of the epithelium with patchy desquamation and deep fissuring

TERTIARY BONE LESIONS

Certain bone lesions occur in yaws endemic areas which are usually ascribed to the infection, although proof of their origin is often lacking These may lead to considerable destruction and deformity Unlike the secondary lesions, they tend to develop in few rather than many bones

The characteristic radiographic pattern is one of well-defined local cortical rarefaction, the rarefied areas are roughly oval and often contain debris or spicules of dead bone. There may also be localized

curious hard thickening of the face on either side of the bridge of the nose known as goundou. In this condition the nasal processes of the maxillae are covered with thickened fibrous periosteum and new bone.

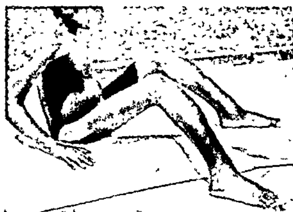


Fig. 70. Deformed tibiae in a case of yaws.



Fig 71. Goundou

Goundou occurs during an attack of yaws usually contemporaneously with other bony changes of secondary type

The joints are not commonly involved, although there may occasionally be some excess free fluid. Epiphyseal changes are not believed to be produced by yaws *per se*

ulceration Healing occurs with the most hideous scarring Treponemata have not been discovered in these lesions but the condition is commonly accepted as a tertiary manifestation of yaws

COURSE AND PROGNOSIS

Yaws is never congenital It is rare in children before the age of one year A few weeks to months after the appearance of the primary lesion, secondary lesions of various kinds, predominantly the granulomatous eruptions, develop and may persist, subside and reappear in succession of overlapping or separate crops for two to three years Secondary bone lesions commonly appear contemporaneously with secondary eruptions After some time many cases become free of the secondary skin lesions, in others they may reappear at irregular intervals for years

It is probable that most cases overcome their infection at this stage and recover completely In others the disease may be resolved during a latent secondary stage In some the disease becomes latent and either slowly disappears or reappears after a long interval either as further secondary eruptions or in tertiary form In others, there is a continu-

develop in a given early case, although it has been said that they appear more commonly in subjects in whom the earlier manifestations were poorly developed

There is often no history of a primary eruption The first sign of the disease may be a crop of secondary lesions In many such cases it is probable that the primary lesion may have receded before ulceration and so been missed

The development of secondary eruptions indicates the spread of the organisms by the blood In some areas, however, autoinoculation may occur due to friction, frequent or persistent contact and moisture

Secondary lesions, especially about the lips or in the soles, may appear in older children and adults who have had more generalized eruptions in early childhood Some of these cases may represent new infections, artificial reinfection with massive doses of infective material has been successful within three years of the appearance of the initial naturally acquired lesion In others the disease may have been latent and relapsed These late recurrences are important in maintaining the infection in a community and illustrate the difficulties of defining the stage of the disease in terms of the duration of the infection

The prognosis of yaws depends on the duration of the disease and the point at which active treatment was administered In the primary and secondary stages treatment is very successful and permanent cure may be achieved Spontaneous recovery may occur at any stage

periostitis with new bone formation, as distinct from the more generalized periosteal changes of the secondary lesions

Local pain is rarely as severe as in secondary lesions and may be absent

Nodules on the skull occur in some cases in the older age groups. These result from irregular thickening and rarefaction of the skull bones, particularly the outer table. Ulceration of the overlying skin may occur with sinus formation. Similar nodules may sometimes be seen on the sternum and the clavicles The latter, and the ribs, may be thickened



Fig 72 Gangosa

Spontaneous fractures of long bones may occasionally occur at the site of tertiary lesions

The most advanced and destructive lesions develop in the face and involve especially the nasal processes of the maxillary bones In some cases the hard palate is destroyed, following ulceration of the associated mucous membrane This condition in its various stages is known as 'gangosa' It occurs irregularly within yaws endemic areas The lips and skin over the maxillae ulcerate, the bone and cartilage beneath are absorbed and ultimately may disappear, and the remains of the upper lip come to border a cavity which may extend to the eyes and through which the tongue may sometimes be seen with the mouth shut The lower lip and most of the skin of the face may be involved in the

history and the peculiar pigmentary changes of pinta should all help in

young childhood, so that the early history may offer little help, unless there is a clear history of primary yaws The circinate papules and roseolar eruption may closely resemble yaws Spontaneous recovery may occur in the early stages as in yaws, the bone lesions are very similar to those of secondary yaws Ulceration of the palate and tonsils and involvement of the nasal bones are common in the tertiary stages

Difficulty may be experienced in separating the late ulcerating granulomata of yaws, in which treponemata are rarely found, from tropical ulcer In the tropical ulcer the exudate commonly contains fusiform bacilli, spirochaetes and pyogenic bacteria in abundance The exudate from the yaws is relatively free from organisms and rarely contains fusiform bacilli

LABORATORY DIAGNOSIS

The treponema Exudate from primary or secondary skin lesions usually contains the treponema, which can be identified most easily by dark-ground examination of a wet coverslip preparation The crust should be removed from the suspected lesion and the surface, if obviously secondarily infected, cleaned with saline It is then lightly scraped, and fluid is gently expressed and examined Dried preparations fixed by passing through a flame can be stained with Giemsa's stain In histological preparations the treponemata are best shown up by Levaditi's silver technique and are to be found in the region of the epithelial papillae

Serological reactions The Wassermann and Kahn reactions become positive in yaws about three weeks after the appearance of the primary lesion, and may reach their maximum intensity in about another month, or sometimes after a much longer period Thereafter they remain strongly positive throughout the disease until the late healing tertiary stages, when they become negative The reactions are weakened and sometimes rendered negative by successful treatment

Simple and rapid flocculation tests such as that described by Ide are now often used in the field investigation of yaws Most of them give results very closely in accord with the Kahn reaction

Cerebrospinal fluid Changes in cell or protein content are very exceptional There are occasionally a slight increase in globulin and a

The effect of treatment on tertiary lesions is slow, but the progress of the lesion may be checked.

DIAGNOSIS

CLINICAL

The clinical diagnosis of an individual case of primary or secondary yaws is usually easy. The co-existence of other cases in an endemic area and the clinical history are important indications. In mass surveys in endemic areas the important feature of clinical diagnosis is to distinguish the infective case which is capable of maintaining the infection in the community. Broadly speaking, infective cases include all those with primary or secondary skin lesions. There may be latent cases which may present no active lesions at the time of examination

It may sometimes be difficult to distinguish certain lesions of yaws from those of syphilis, pinta or bejel.

Skin lesions due to causes other than treponemata should present little difficulty. Pus infections, scabies, fungus infection, various dermatological conditions such as lupus, seborrhoea, acne and psoriasis may cause some confusion. The nodular lesions of leprosy may closely resemble yaws in some cases and may exist contemporaneously. Leishmanial skin lesions, particularly espundia, may be mistaken for tertiary yaws, but should be distinguished by finding leishmania in the tissues

The differentiation from syphilis may be difficult, the conditions *may occasionally exist contemporaneously. Yaws is not congenital;* lesions in the new-born or in very young infants should be regarded as syphilis, not yaws The primary lesion of yaws is extragenital, only slightly indurated and if near a moist surface may be covered with a crust; in syphilis it is commonly genital, firmly indurated and not crusted The history of a primary lesion is much commoner in yaws than syphilis The position of the primary and the age of onset should be important leads to the diagnosis of yaws from syphilis The age group at the onset of syphilis is much older than in yaws Although the macular and papular lesions of yaws may closely resemble those of syphilis, the florid primary and secondary lesions have no syphilitic counterpart. The mucous membranes proper are only occasionally involved in yaws, commonly in syphilis. Changes in the spinal fluid are common in syphilis, rare in yaws (see below). Yaws is much more common in rural populations

The diagnosis of yaws from pinta may be difficult, especially in areas where the conditions co-exist The lesions of the hands and feet, for instance, may be indistinguishable. The early stages of pinta usually present little difficulty. The tissue reaction is less active than that of yaws. The primary lesion progresses more slowly and does not develop

agreement that the antibiotic is safer, more easily administered and more effective than any other treatment

EFFECT OF TREATMENT

Treatment with penicillin has a remarkable effect on primary and secondary skin and bone lesions in individual cases Clinical healing is sometimes complete in a week or a fortnight

Single dose treatment may produce equally startling results but to be permanently effective, full dosage is necessary

In mass treatment, single dosage therapy is adequate provided some follow-up is carried out

Relapses are practically certain after incomplete or single dosage They may also occur after a full course of treatment with any therapeutic agent, but the chance of relapse in a given case after proper treatment is small Relapses with the development of active ulcerating lesions tend to occur most frequently in the first year after treatment Full therapy is required in relapsing cases

CONTROL

Undoubtedly the most satisfactory way to control the spread of yaws in a given district is the identification and treatment of infective cases Mass treatment (usually with penicillin) must be well organized, economic, regular and continuous in order to cover relapses and infective lesions appearing in missed latent cases The usual field technique includes census of the population, followed by a diagnostic survey, followed in turn by mass treatment, the establishment of treatment centres and regular visits by technicians trained to recognize fresh infective cases and treat them

Where there are only a few cases with active lesions, it may be possible to segregate them during treatment and so reduce the spread by direct contact In a highly endemic area this is impossible and the continuous control of infective cases by chemotherapy is the only effective measure Improvement in hygiene, control of flies, the use of clothing and avoidance of unnecessary contact should also be attempted as a long term policy, largely dependent on education

positive Lange colloidal gold reaction resembling that of syphilis. There may also be a small increase in lymphocytic cell numbers.

In the vast majority of cases the Wassermann or Kahn reaction is negative in the cerebrospinal fluid even when that in the blood is strongly positive

Blood There are no characteristic changes in cellular or chemical content

Attempts at animal inoculation and bacteriological identification of the treponema can be carried out only by those well acquainted with the techniques and should be left to them.

TREATMENT

Penicillin is the drug of choice in the treatment of yaws either in individual cases or in mass campaigns

It is most commonly given intramuscularly in the form of procaine penicillin G in oil plus 2 per cent aluminium monostearate (P A M).

1 For treatment of individual cases the following dosage regimes are advised·

Adults	1 2 million units, intramuscularly, given twice, with an interval of 3 to 5 days between doses Total dose 2 4 million units
Children 5 to 15 years	0.6 million units intramuscularly, given twice, with an interval of 3 to 5 days between doses Total dose. 1.2 million units
Children under 5 years	0 3 million units intramuscularly Total dose 0 3 million units

2 For mass treatment campaigns, adults and children aged 5-15 years are commonly given a single intramuscular dose of 1 2 and 0.6 million units respectively. Children under the age of 5 receive 0 3 million units

Other antibiotics, including aureomycin and chloramphenicol, are also effective and may be given orally Since the standard dosage regimes recommended take longer to administer than those of penicillin, these more expensive drugs are rarely used for other than the treatment of individual cases

Former popular chemotherapeutic compounds including arsenicals such as neoarsphenamine mapharsen and acetylarsan, and bismuth preparations, such as bismuth subsalicylate, sodium potassium bismuth tartrate (B S P T) and bismosol, are being used on a steadily diminishing scale, as penicillin comes into wider use There is general

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